THE American Journal OF Gastroenterology

VOL. 27, NO. 3 MARCH, 1957

Panel Discussion on Diseases of the Stomach and Duodenum

Histoplasmosis and the Gastroenterologist

The Present Management of Ulcerative Colitis with Special Emphasis on Sprue Diet

Glutamic Acid in the Treatment of Hepatic Coma and Its Relationship to Blood Ammonia Levels

Tubeless Gastric Analysis

Twenty-second Annual Convention
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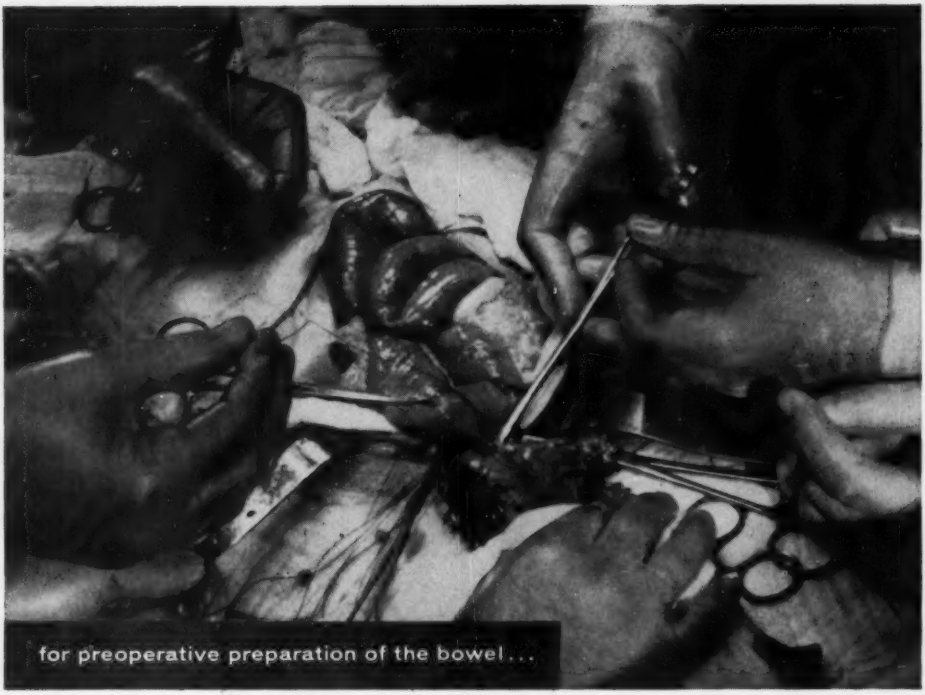

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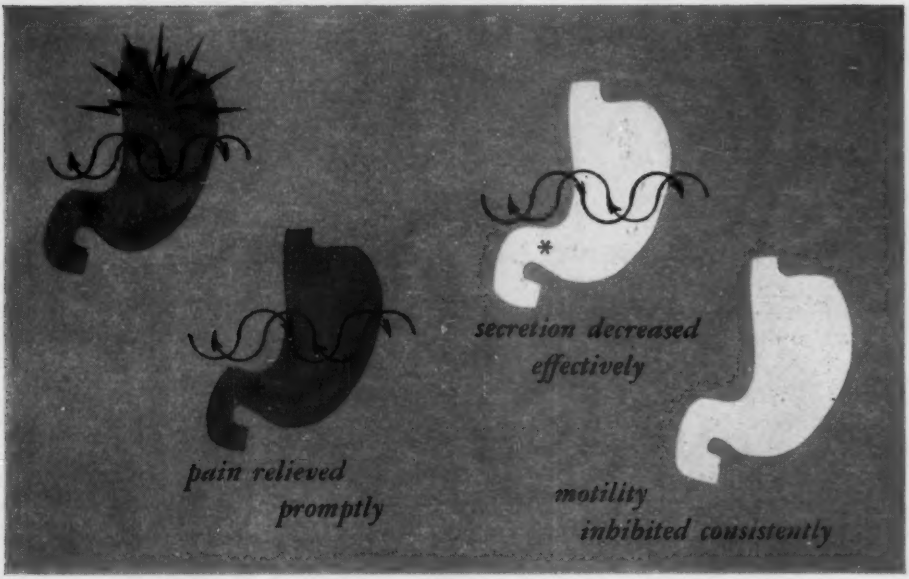

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THE American Journal OF Gastroenterology

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The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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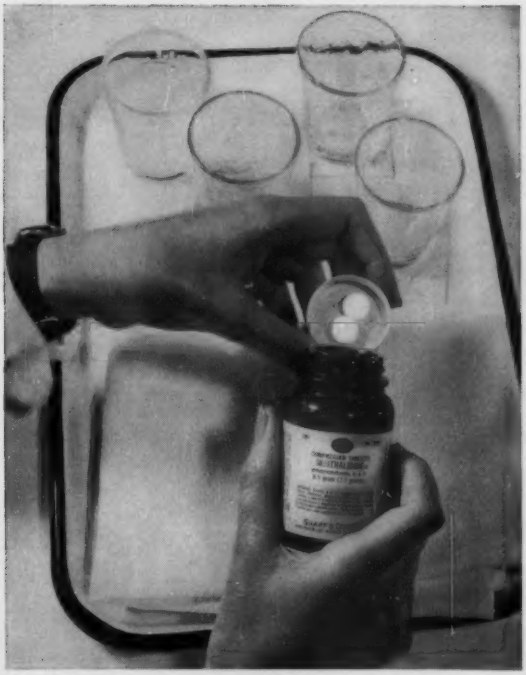

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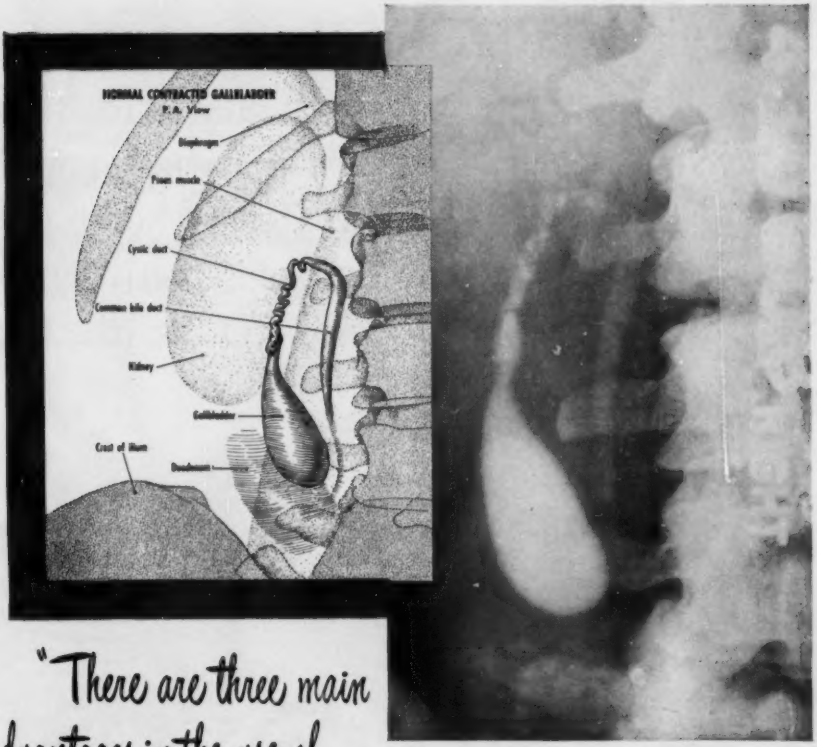

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THE American Journal OF Gastroenterology

A monthly journal of Gastroenterology, Proctology and Allied Subjects
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VOLUME 27 MARCH, 1957 NUMBER 3

PANEL DISCUSSION ON DISEASES OF THE STOMACH AND DUODENUM*

LINN J. BOYD, M.D., F.A.C.P., F.A.C.G. (Hon.), Moderator†

GEORGE B. JERZY GLASS, M.D., F.A.C.P., F.A.C.G.‡

FRANK J. BORRELLI, B.S., M.D., F.C.C.P., F.A.C.R., F.A.C.G.§

FRANCIS D. SPEER, M.D.¶

and

RALPH COLP, M.D.**

New York, N. Y.

Dr. Linn J. Boyd:—The panel discussion will be on the subject of diseases of the stomach and duodenum.

I should first like to introduce the panel members. On this end of the platform is Dr. George B. Jerzy Glass, Associate Professor of Medicine, in charge of the gastroenterological laboratory of New York Medical College.

The next gentleman is Dr. Frank J. Borrelli, Director of Roentgenology in the same institutions mentioned in connection with myself, and I understand for some time an officer of this College, so I won't spend any further time on him.

Next is Dr. Francis D. Speer, Professor of Pathology and Clinical Pathology, New York Medical College, and Flower-Fifth Avenue Hospital.

The last gentleman is Dr. Ralph Colp, Professor of Clinical Surgery, New York Medical College, Flower-Fifth Avenue Hospital.

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*Presented before the Third Annual Convention of the American College of Gastroenterology, New York, N. Y., 15, 16, 17 October 1956.

†Professor and Director of Medicine, New York Medical College.

‡Associate Professor of Medicine, New York Medical College.

§Professor and Director, Department of Radiology, New York Medical College.

¶Professor of Pathology and Clinical Pathology, New York Medical College.

**Professor of Clinical Surgery, New York Medical College.

In order to get this discussion under way, I have asked each of these participants to discuss a topic which I have assigned to them, and to spend five or six minutes on that particular subject. I have selected the topics because I thought they were identified with studies in the particular field. After that we shall rapidly go around with questions and anwsers. For additional questions from the floor, I understand that there are pads placed around and you can send your questions up.

The topic which I selected for the first two, I chose because I thought there were differences of opinion, and I thought maybe we could get a little discussion started right off the bat.

I have asked Dr. Glass to discuss gastric atrophy, its significance and diagnosis, and I have asked him to bring a few slides which might help illustrate the problem. Dr. Glass!

Dr. George B. Jerzy Glass:—The problem of gastric atrophy has become of more interest during the last years, although it has been known since 1870 when Fenwick discovered gastric atrophy in a patient who died of pernicious anemia. About 30 years later Faber in Denmark again became interested in atrophic gastritis and gastric atrophy but his studies were somewhat forgotten. Though these two conditions are clinically and pathologically different, this distinction has become obliterated, owing to gastroscopists. This is due to the fact that on gastroscopy the atrophic mucosa of gastric atrophy and that of atrophic gastritis looks much the same.

Undoubtedly gastric secretory function is diminished in both conditions. Both in gastric atrophy and atrophic gastritis you find gastric anacidity, and a decrease or abolishment of secretion of other glandular products of the stomach, i.e. pepsin and glandular mucoprotein. Also cytologically both are similar. In both you find large bland columnar cells which were first described in atrophy of gastric mucosa in pernicious anemia, and which may be due not to gastric atrophy, but rather to Vitamin B_{12} deficiency being the result of gastric atrophy.

Gastric atrophy results in abolishment of secretory function of gastric glands and this includes abolishment of secretion of intrinsic factor. This results in defective intestinal absorption of Vitamin B_{12}, hence, pernicious anemia. On the other hand, gastric atrophy may be the last stage of atrophic gastritis, its ultimate sequella.

There are data available which indicate that gastric atrophy may be considered as a precursor of gastric cancer. This statement is based on some data which I should like to show in the slides.

(Slide) This slide shows that in 5,777 patients with pernicious anemia the incidence of clinical diagnosis of concomitant gastric cancer, amounts on the average to 1.9 per cent, as computed from 17 different publications. This, of course, is an incidence which statistically is not very significant.

(Slide) This slide shows, however, that if the investigations are done on patients who died, the picture will look quite differently. In the two large series of cases from Minnesota and Denmark listed in this slide, you will notice that there is a very significant relationship between pernicious anemia and coexistent gastric carcinoma on autopsy. In patients with pernicious anemia the incidence of gastric cancer is about 12 per cent, which is more than 20 times the average occurrence of gastric carcinoma on autopsy.

(Slide) There is another element which is of importance for proving this association. This slide shows that the site of gastric cancer in patients with pernicious anemia is somewhat different from that which is the usual one. Normally about 50 to 75 per cent of gastric cancer cases are located in the pyloric area and only 20-30 per cent in the fundus. In patients with pernicious anemia, this proportion is reversed and the main site of cancer is the fundus and body of the stomach. Since this is the area where gastric atrophy occurs this speaks again for the relationship of gastric cancer to gastric atrophy of pernicious anemia.

Another point which is important is that in lower animals one does not find cancer of the stomach. In rabbits or rats it is exceedingly rare to find this condition, but also one cannot produce gastric atrophy experimentally in these animals and one cannot find spontaneous gastric atrophy in them. Those two diseases, gastric atrophy and gastric cancer, do not exist in lower animals, which is again rather an interesting point.

What the possible mechanism for the development of malignancy from gastric atrophy is, we do not know. One possible mechanism is the development of gastric cancer from sites of intestinal metaplasia in gastric mucosa, which is exceedingly frequent and extensive in gastric atrophy.

Another point of origin might be large bland columnar cells found in gastric atrophy. Cytological examination of gastric smears in patients with gastric atrophy revealed frequent mitosis in these large cells. According to investigators from Chicago, these abnormal columnar cells could be precursors of malignant cells of gastric cancer. This point requires further exploration.

The diagnosis of gastric atrophy is not easy. Gastric anacidity does not always mean gastric atrophy. About 30 per cent of people over 50 have gastric anacidity and many of them produce Castle's intrinsic factor in adequate amounts to provide for normal intestinal absorption of Vitamin B_{12}. Moreover, "gastric anacidity" is a rather vaguely defined term. First of all, only histamine fast anacidity is significant. Even here, however, the interpretation is complicated by the fact that, as shown in England, if one repeats histamine injections at intervals of one-half hours twice or three times you may find hydrochloric acid present in 5 per cent of initially anacid cases.

Moreover, titration of free acid with Toepfer reagent is not adequate for study of anacidity. Since pH 3.5 is the limit of titration of free HCl with Toepfer

reagent; pHs above 3.5 mean anacidity, which is erroneous. When a small amount of acid is secreted it may drop the pH from 7.0 to 5.0 or 4.5 only. Such pH indicates the presence of some acid in the stomach buffered by nonparietal secretions. Toepfer's reagent would indicate here complete anacidity. One can consider, therefore, as real anacidity only such conditions in which, after repeated histamine injections, the pH would not decrease below 6.0-6.5, i.e. the pH of mucus secretions of the stomach.

Dr. Boyd:—I will interrupt you there, Dr. Glass. We have to move on, and we will come back.

The second question, which I am addressing to Dr. Speer, is almost the same, namely, the relationship of atrophic gastritis to polyposis and gastric carcinoma.

Dr. Francis D. Speer:—Chronic atrophic gastritis is a fairly common lesion in adults over 45 years of age, as you know, and whether you call it gastric atrophy or atrophic gastritis probably depends on your political party. (Laughter)

Its etiology is, of course, unknown at present, though there is rising suspicion today that it will turn out to be a deficiency disease. Its microscopic anatomy includes many things. If atrophy is predominant, without inflammatory changes, we are likely to use the term gastric atrophy, whereas if we find eosinophilic and lymphocytic cell infiltration and slight fibrosis, etc., we call it atrophic gastritis. Both of the conditions are associated with varying degrees of intestinal gland metaplasia.

You will find great variety as to location and degree; however, the lesion seems to be primarily degenerative and is frequently, though not always, associated with reduction of hydrochloric acid secretion.

Symptoms, as you know, are frequently slight, and may not be present at all. At present, with few exceptions, there is no specific treatment.

While numerous studies purport to show the relationship of these various lesions termed "atrophic gastritis" or "gastric atrophy" to gastric cancer, careful studies of Hebbel and others certainly show no really impressive relationship between the two. In a series of gastric cancer cases, 45 per cent showed antral gastritis, and 55 per cent fundal gastritis, a combination of lesions up to about 70 per cent. A series of lesions of nontumor-bearing stomachs of the same age group, showed atrophic gastritis, and the percentage also was 72. Therefore, I think we may conclude that atrophic gastritis as an independent condition, mind you, has no proven relationship to gastric cancer.

When we come to consider the relationship of gastric cancer to the atrophic gastritis which is a very intimate part of pernicious anemia, we find an entirely

different situation. The following statistical data is of importance, and it is pretty much the same as Dr. Glass has shown you:

1. Gastric polyposis and gastric cancer are both more frequent in patients with pernicious anemia than in adults of the same age group in the general population. This is estimated all the way from 3 per cent to as high as 12.3 per cent as reported by Kaplan and Rigler. On the other hand, gastric cancer has an incidence of about 1 per cent in individuals with achlorhydria but without pernicious anemia, so that you can have three to 12 times the incidence of gastric cancer in pernicious anemia as you have in other achlorhydric patients.

2. The second point of significance would be that in a series of gastric cancer cases, patients with true pernicious anemia occur in high incidence.

3. The third point would be that in pernicious anemia patients with tumor, over 60 per cent of the tumors occur in the stomach and, of course, they occur more commonly in the fundus of the stomach.

We may conclude, therefore, that there is a very interesting relationship between pernicious anemia and atrophic gastritis, and gastric polyposis, and gastric carcinoma; however, we are unwilling to believe that it is the atrophic gastritis that is the essential precancerous lesion in pernicious anemia, for the following reasons:

1. There is by no means enough difference between the atrophic gastritis of pernicious anemia and that in hypo- or achlorhydric, nonanemic cases to be significant.

2. The microscopic changes in the gastric mucosa do not deserve the term "precancerous" or "carcinoma *in situ*". The intestinal metaplasia is part of the picture of atrophy, and while some of the epithelial cells do show atypical features and mytotic features, these are essentially the anaplasia of degeneration and not that of neoplasia. There seems to us to be no more reason for referring to these changes in the stomach, particularly in the fundus, as "precancerous" than there is to refer to the squamous metaplasia of the endocervical glands and all of the associated changes, inflammatory changes of the cervix uteri as "precancerous", which they are not. Everyone knows they are not precancerous and have nothing to do with carcinoma *in situ*. The changes in the stomach are very similar.

If it is unwise, therefore, to consider the changes in the gastric mucosa in pernicious anemia as the cause of increased polyposis and of cancer, what, then, may be related to these conditions? The following suggestions seem to be important:

1. Effective treatment of pernicious anemia in the last 25 years has kept many people alive so that they can develop cancer. This, however, we do not consider most important.

2. There may be common hereditary factors in the pernicious anemia case and in the case which develops a gastric carcinoma.

3. The deficiency disease that is pernicious anemia may allow the development or activation of intrinsic carcinogens not activated in nonpernicious anemia cases.

4. We also might suggest the treatment of pernicious anemia, that is, liver therapy and vitamins, may be carcinogenic. It will be very interesting to see whether the high incidence of gastric cancer persists in cases treated exclusively by Vitamin B_{12}.

These suggestions up to the present time have yielded no significant findings to explain the high incidence of gastric polyposis and gastric cancer in pernicious anemia, it is true. They are emphasized, however, to draw attention away from the gastric atrophy, or atrophic gastritis, which does not seem to be the important problem in the etiology or pathogenesis of polyposis or gastric cancer.

It can still be admitted that the pernicious anemia cases should be periodically examined by gastroscope and by x-ray to detect, if possible, early polypi and early malignancy, but none of us believes this will help us with the fundamental problem of gastric cancer, because by such means it is doubtful whether one could discover one-tenth of 1 per cent of the cases of gastric carcinoma.

Dr. Boyd:—I warned you the first two speakers might disagree slightly with each other.

The third speaker, I think, will disaggree with the entire audience. I think everyone has his own answer to the question I will address to him. I have divided it into two parts:

a. When and why is duodenal ulcer missed roentgenologically, when it is actually present?

b. When and why is it diagnosed when it is actually absent? (Laughter and applause)

Dr. Frank J. Borrelli:—It would take a long morning to get that one answered.

I think, it is quite an interesting problem in which most of us are interested. We are all confronted with it; that is, how difficult is it to be sure, when one is studying the stomach and the duodenum?

I am glad Dr. Boyd gave me one minute to think this one over, but I think the trouble, as most of you know, usually is carelessness, and for that, of course, there is no excuse. If one doesn't know better, that might be understandable, but to be negligent and incomplete in the examination that is inexcusable.

You are aware that you may see something in the erect position that you do not see in the prone or semiprone position. You may find lesions in one oblique view and not in the other, and further, you may demonstrate lesions in a lateral view in one case, while in others it is the most important view. You all know how fluoroscopy is absolutely necessary and that serialograms and even high intensification fluoroscopy, which is not economically available to most doctors, have helped us in some problem cases where the clinicians are breathing down our backs—especially Dr. Glass and Dr. Boyd. (Laughter)

In so many words, I feel that it is incompleteness of examination that is responsible for the errors, positive or negative, as you asked in your question.

Another thing is the lack of clinical correlation. Of course, most gastroenterologists do, fortunately, see their patients more carefully than the average roentgenologist. I am not saying that the average gastroenterologist knows more x-ray interpretation than his fellow radiologist.

I felt there was a little jab at the radiologists here by Dr. Berry, when he said that diagnoses were only made clinically. I agree, in most instances, the clinical examination is important, yes, but I think most of you will admit the x-ray interpretation is very, very useful. In my estimation it is most helpful, but it is almost important that the clinical correlation be checked. For instance, in some of these polypi or hypertrophy of the rugae that Dr. Speer and Dr. Glass are talking about, one cannot be sure at the first roentgenographic examination. It is a routine in our department that no polyp is ever diagnosed unless it has been seen the second time during another examination.

So, Dr. Boyd, I think that your question is well put, inferring that ulcers may be missed or found when not actually present. Satisfactory examination in all positions, and with all various contrast and double-contrast media, with proper fluoroscopy is absolutely necessary. I think the best answer to your question is that ulcers are most often missed or not seen because of the lack of thorough complete proper roentgenographic examination by well trained examiners.

Dr. Boyd:—In asking Dr. Colp his question, I asked him if he could bring some slides. He might summarize his viewpoint, and that is a debatable question: the present status of vagotomy in the treatment of duodenal ulcer.

Dr. Ralph Colp:—(Slide) We have been doing subtotal gastrectomy of the Billroth II type removing about two-thirds or three-quarters of the stomach, since 1923, performing an anterior gastrojejunostomy. Naturally, an operation of this magnitude cannot be applied to every patient, and we have no hesitancy in the poor risks, the elderly patients over 65, and the obese, and those with cardiovascular diseases, in performing a gastroenterostomy, realizing full well the incidence of gastrojejunal ulcer. That we have been ultraconservative in this regard, we have no doubt, because many of these patients have subsequently had subtotal gastrectomy following the development of a jejunal ulcer.

This slide represents a five-year study starting in 1946 and going through 1952, with a follow-up of one to nine years. You will see that during this period 101 gastroenterostomies were done, 28 without vagotomy, and 73 with vagotomy, and in the subtotal gastrectomies, 224 without vagotomy and 217 with vagotomy.

It is interesting to note the mortality of 5 per cent in the gastroenterostomy series, showing that we were dealing with poor risk patients. In the subtotal gastrectomy series, looking at the mortality, one was lost, and two were lost in the subtotal and vagotomy series. One patient died of a bronchopneumonia and pancreatitis, on the fifth day, I believe, and one of the two died of embolus, and the other from a necrotizing pancreatitis. These three mortalities were proven by postmortem examination.

When we first began to do vagotomy, we found patients with a very high preoperative gastric acidity had bleeding tendencies. We then gradually extended our indications. It is undoubtedly true that when you perform a vagotomy, there is a higher incidence of immediate postoperative complications manifested by vomiting, gastric dilatation, and pulmonary complications, and sometimes a troublesome diarrhea, but none of these were responsible for any mortality.

(Slide) This shows a follow-up, and we have stated that patients when seen at the last follow-up, if they are considered satisfactory, are counted by us as satisfactory; if not, we count them "unimproved". Those who were counted as satisfactory have absolutely no complaints whatsoever.

I was not responsible for these follow-ups because I feel that the operator is prejudiced, and we always have three men go over the patients. I am indebted to Dr. Weinstein, the late Dr. Druckerman and Dr. Silagy for these results. You will see that 83 per cent of the patients were well, and 7 per cent of them were not well, and had symptoms such as marked diarrhea, or they had some pain, or they were generally uncomfortable, and yet repeated x-rays failed to show any evidence for their unimprovement.

Among the unsatisfactory ones, the greatest number were contributed by an incidence of 7.7 per cent of gastrojejunal ulcer in this series of 206, whereas there was one gastrojejunal ulcer in the subtotal with vagotomy, an incidence of 0.5 per cent. There were no suspected ulcers. There were three among the "other causes". One had a persistent diarrhea, and a couple had pain. None had a hemorrhage.

(Slide) This shows the incidence of gastrojejunal ulcer in gastroenterostomies without vagotomy, followed one to six years, with an incidence of 15 per cent; gastroenterostomies with vagotomy, one to eight years, 12 per cent. That is not a great deal of difference. Subtotal gastrectomy, followed one to nine

years, an incidence of 7.7 per cent, and subtotal gastrectomy with vagotomy, an incidence of 0.5 per cent at present.

Now we feel that essentially the addition of infradiaphragmatic vagotomy provides added protection against the incidence of gastrojejunal ulceration at the risk of increased incidence of immediate postoperative complications and an incidence of about 10 per cent diarrhea. In one case this was incapacitating, and in the others it was not.

I will emphasize again, when I say "up to the present", because you all know that recurrences can be noticed 15 to 27 years after any of these operations, and the ulcer history of a patient encompasses his lifetime. By any test, however, in the method of subtotal gastrectomy with vagotomy, there is a much larger incidence of achlorhydria than there is with subtotal gastrectomy alone, because not only has the hormone phase been removed, but the vagal phase has been interrupted, and if there is a greater incidence of anacidity, you will remember that "where there is no acid, there is no ulcer". Undoubtedly there will be less acid with the combined procedure than with the single procedure.

Dr. Boyd:—Thank you, Dr. Colp. Dr. Glass, I will give you a minute or two to state why you think Dr. Speer may have gone too far.

Dr. Glass:—My main objection would be that Dr. Speer's point of view is the one of the pathologist.

The introduction of the suction biopsy instrument for the study of gastric mucosa has allowed the investigators to study the development of the atrophic process from the initial stage of slight superficial atrophic gastritis through the stage of atrophic gastritis, to the final stage of gastric atrophy.

This (indicating apparatus before him) is the instrument. If anyone is interested in seeing how it works, at the end of the meeting, I will show it to you. It is the Wood-Doig model, as modified by Rubin.

On suction biopsy, stained gastric mucosa in gastric atrophy looks different from that in atrophic gastritis. The gastric mucosa in pernicious anemia usually shows lack of lymphocytic infiltration. Intestinal metaplasia is much more extensive in gastric atrophy than in atrophic gastritis. Moreover, as shown by British investigators in Edinburgh, the number of preserved parietal cells in atrophic gastritis is much larger than in gastric atrophy in pernicious anemia, where they are hardly present.

Therefore, although what Dr. Speer has said is absolutely true in regard to the relationship of atrophic gastritis and cancer of the stomach, I don't think it holds also for the relationship between polyposis and cancer of the stomach and gastric atrophy.

Dr. Boyd:—Do you concede, Dr. Speer, or do you not?

Dr. Speer:—I think we have admitted that there are quantitative changes between atrophic gastritis and the gastric atrophy in pernicious anemia. We, however, feel, that by any method, whether you do it during life or you do it on the surgical specimen, or you do it at autopsy, you will find extreme degrees of gastric atrophy in nontumor, nonpernicious anemia cases, as well as in pernicious anemia cases. This, to our mind, gets to be the problem of the hen and the egg, in relation to polyposis and cancer, and if we thought something was there that deserved local study, we would concede, but we think that the problem of gastric cancer *per se*, and in the pernicious anemia cases, does not primarily relate to the changes in the stomach. They are broader than that. They are systemic; they are biologic; they relate to inheritance, and that is the reason for our interest in these broader phenomena.

Dr. Boyd:—The subject might be pursued further, but I think we had better drop it because there are other things to which we wish to make allusion.

Dr. Glass, what is your attitude toward so-called urinary tests for the evaluation of gastric secretion? Do they have significance?

Dr. Glass:—I would say, yes. These tests constitute a screening method for the presence or absence of gastric acid, pepsin, and intrinsic factor in the stomach. The first of these, the quinine test, developed by Segal, which all of you certainly know, detects the presence of hydrochloric acid in the stomach. There is a new modification of this test also developed by Segal, in which, instead of quinine, the azure dye is used. This test is exceedingly easy, and one can tell rapidly whether hydrochloric acid is present in the stomach or not, within a few minutes of laboratory work and after having collected the 2-3 hours urine. This test is good only when it is positive. The negative test carries up to 20 per cent error, especially because the usual gastric stimulant applied in this test, caffeine, is certainly not adequate for eliciting maximal gastric secretory output in the hypoacid or anacid stomach.

The second test, which is very important, is the urinary test for the presence of intrinsic factor in the stomach. If the intrinsic factor is present in the stomach and you give radioactive B_{12} by mouth, this will be absorbed in the gut and deposited in the liver, where we can locate it later on by the surface scintillation scanning of the cutaneous projection of the liver. I have a slide on our method of measurements of the hepatic uptake of radioactive Vitamin B_{12}—may I show it?

Dr. Boyd:—One-half minute.

Dr. Glass:—Then, better not! If at the same time, however, or 2 hours later, one injects a large dose of nonradioactive B_{12}, then one part of radioactive B_{12}, instead of running into the liver, will pass into the urine where it can be detected by counting the urinary radioactivity. The positive test rules out the diagnosis of complete gastric atrophy because it shows presence of intrinsic

factor in the stomach. On the other hand, in gastric atrophy, intrinsic factor is not produced in the stomach, and radioactive B_{12} will not be absorbed in the intestine. The absence of radioactivity in the urine under these circumstances will speak for gastric atrophy.

The third test, is the uropepsin test for determination of the secretion of pepsin in the stomach. There is an exocrine-endocrine partition of pepsin in the stomach so that one part of pepsinogen goes into the blood, where it can be easily determined, and one part of it is thereafter excreted as uropepsin in the urine. If the 24-hour output of uropepsin in the urine is determined, one knows the rate of production of pepsin in the stomach.

These three tests can, therefore, easily differentiate between high and low output of gastric secretion, and screen defective gastric secretion. They should not be used for the purpose of detailed assessment of the secretion of each of the gastric secretory products, however, which can be done only by comprehensive gastric analysis.

Dr. Boyd:—Thank you, Dr. Glass. Again I have a different topic. But first, Dr. Speer, do you agree with what Dr. Glass said, or not?

Dr. Speer:—No.

Dr. Boyd:—Do you accept the concept of antral gastritis as a clinical or pathological entity?

Dr. Speer:—We certainly have seen it as a pathological entity and, from our experience with differential diagnosis, it certainly seems to have practical clinical significance. Naturally it comes up in the problem of differential diagnosis of cancer and of, say, chronic prepyloric ulcer. We think that it should be preserved as a disease entity.

Dr. Boyd:—Dr. Borrelli, what do you think of the clinical significance of the x-ray diagnosis of prolapse of the pyloric or gastric mucosa?

Dr. Borrelli:—Actually it was first reported—I guess, just after I was born—but apparently it was put on the shelf. I think Schmeiden was the first one who reported on prolapse, and in my school days we heard very little about it. Recently, however, it has become popular again. I am sure prolapse has occurred all the time.

Some prolapse is definitely clinical causing pain, bleeding, and what not. By x-ray the roentgenogram simulates a picture not unlike what Frank Speer mentioned, an antral gastritis, unless you study it carefully. The hypertrophy of mucosa will invaginate or prolapse into the first portion of the duodenum and give you the so-called umbrella-like appearance, or the curvalinear base of the cap.

There is no question in my mind that the condition occurs and it is clinical, but I think that too many are seeing a lot of mucosa and then, when the surgeon

opens up the stomach he doesn't find an explanation of the symptoms. Therefore prolapse is not uncommon, may cause pain, bleeding, and even signs of temporary obstruction, but it may not be easy to demonstrate at all times.

Dr. Boyd:—Dr. Colp, we come to you again. So far as you are concerned, what do you feel are the positive indications for surgical intervention in: a. nonbleeding gastric ulcer, b. nonbleeding duodenal ulcer, and c. gastrojejunal ulcer, nonbleeding. I would rather you would mention nonbleeding. I will ask you about bleeding later.

Dr. Colp:—I think that surgeons, gastroenterologists, and medical men are fully agreed as to the indications for surgery in duodenal ulcer. The acute phase, that of perforation and hemorrhage, of course, we will not discuss. In the chronic phase, with repeated hemorrhage, pyloric duodenal stenosis, which leads to persistent vomiting, and in those cases that have been treated over a great many years or which no longer respond to medical treatment, surgery is indicated.

Now, when we come to gastric ulcer, I think that you and I see this problem a little differently. I feel that every gastric ulcer, excepting the small acute ulcers which respond rapidly to medical treatment, should be operated upon by a radical procedure, namely, subtotal gastrectomy.

Gastrojejunal ulcer is never cured medically, and the symptoms which may be treated and held in abeyance for a while, are well known, but the indications which necessitate surgery in gastrojejunal ulcer, are bleeding, perforation, pain, and obstruction at the stoma due to scar and ulceration, and the occurrence of gastrojejunocolic fistula.

Dr. Boyd:—I imagine Dr. Colp's viewpoint on surgical intervention and on gastric ulcer will be received with mixed feelings. I remember attending a symposium two years ago in which different surgeons gave their views on surgery of gastric ulcer, and held very similar opinions, but two of them drank milk and cream before they went to the platform. They admitted it made a difference who had this ulcer. (Laughter)

Dr. Glass, again, are there any methods, or do you think there is any value in attempting a mass screening for the early diagnosis of gastric cancer?

Dr. Glass:—I think there is some value in it because I believe that gastric atrophy may be a precursor of gastric cancer and therefore, if one looks for gastric atrophy, one screens the gastric cancer.

If you do the urinary resin test for gastric acidity or determine uropepsin output you can pick up the group of patients with impairment or abolishment of gastric secretion. The group may then be submitted to a close examination to determine whether they have gastric atrophy. This can be done by comprehensive testing of gastric secretion which will test not only for anacidity, but

also for the absence of other secretory components derived from glandular elements of gastric mucosa, including intrinsic factor.

Once gastric atrophy is diagnosed, patients should be periodically checked by x-ray and gastroscopic examination, every six months, I would say, which would probably represent the best way of screening gastric cancer. Something along these lines actually has been started in Dr. Wangensteen's clinic by Dr. Hitchcock. These authors started about five years ago, and they have now about 12,000 cases which they have screened and out of which some 16 or 18 cases of gastric polyps and gastric cancer were detected, at a completely asymptomatic stage.

Dr. Boyd:—Do you think gastric analysis should be broadened? Is there still a place for gastric analysis, first, and second, should it be broadened?

Dr. Glass:—I strongly believe that gastric analysis is most important for detection of gastric hypersecretion and hyposecretion, as well as gastric atrophy, and that it should be comprehensive. If one tests for hydrochloric acid only and is satisfied with this examination, one behaves as if he were, let's say, satisfied with a liver work-up which is restricted to the determination of the thymol turbidity only. Since one does 10 or 12 liver work-up tests or several kidney function tests, one should also apply the same reasoning to testing gastric secretory function. The comprehensive gastric secretory tests should include testing gastric secretion both after humoral stimulus, i.e. histamine, and central vagal stimulus, i.e. insulin. Not only hydrochloric acid, but also the other nonparietal components should be determined such as pepsin, mucoprotein, and mucous fractions of surface epithelial origin.

Recently we have developed a most comprehensive analysis of gastric secretion by means of paper electrophoresis. I have one slide which I would like to show.

(Slide) The upper tracing in this slide shows a paper electrophoregram of a normal human gastric juice which contains 8 peaks corresponding to various mucus substances and enzymes of gastric juice. The lower tracing shows what happens in gastric atrophy. Here you see only three peaks, and all of them represent components of surface epithelial origin. All the other peaks, which derive from gastric glands, are absent because of atrophy. This pattern is absolutely pathognomic for gastric atrophy and you don't find it in any other situation. Therefore, here is another example of the importance of gastric analysis for detection of gastric atrophy. I believe, therefore, that modern gastric analysis is as important a tool in clinical investigation as the modern liver or kidney function tests, provided that it is not limited to the obsolete study of gastric acidity only.

Dr. Boyd:—Going back to Dr. Colp again, in order not to break your earlier thought, what about bleeding in these lesions we have mentioned—the indications for surgery?

Dr. Colp:—I think the important thing in bleeding is, first of all, to try to make a diagnosis as to the source.

So far as bleeding from esophageal varices is concerned, a great many of these can be controlled by the Blakemore tube. Bleeding gastric ulcer, in our experience, will, if treated medically, have a mortality of 25 per cent. Bleeding duodenal ulcer will vary according to the hospital in which you gather your statistics. Statistics gathered from patients from the waterfront, and flop house areas recently resulted in an appreciable mortality in the radical operation for bleeding ulcer. This cannot be compared with the statistics on the service of a large voluntary hospital in which there are bleeding duodenal ulcers, to be sure, but not the same type, because there the patients are in better condition.

I do not feel that bleeding from a duodenal ulcer should call for immediate surgery. I think that these patients should be given adequate transfusions and watched, and, if they hold their blood, surgery should be deferred until such time as they have had adequate convalescent care, when this operation can be done with a mortality of less than half of 1 per cent; however, if they do not stand the test of transfusion, they should be explored without further ado. Along with that type of patient is the patient who has stopped bleeding and then, after three or four days after the cessation of the hemorrhage, immediately starts to bleed again, because I think in that type of patient you may predicate an open vessel in the duodenal ulcer.

So, our attitude is that these patients, if possible, should be x-rayed, and an attempt made at a diagnosis and, if they are in categories that can be treated medically, they certainly should be so treated. If they are not, they should be treated surgically. I think one of the most important things is to have these patients seen by a team consisting of a surgeon, a gastroenterologist, and a medical man, so that you have two people who will restrain the hand of the hungry resident who today wants to do a bleeding duodenal, or a bleeding gastric, or any kind of ulcer, the minute it enters through the portals of the emergency room. If that is the case, it might be appropriate to have the same inscription that Dante had over the gates of hell: "Abandon ye all hope who enter here".

Dr. Boyd:—Dr. Borrelli, I passed over a question on duodenum diverticula. How often would you say they are discovered completely accidentally in a routine check-up, or how often do you think they have any clinical significance?

Dr. Borrelli:—I think most of the cases I have seen were not diagnosed as such when they were referred to the department. I would have to dodge that question a little bit because we have not done a routine survey, as some have; on the other hand, I think that most of our cases might be considered routine because as soon as an intern or resident sees a patient who belches once or twice, the patient is referred for a gastric series. So, I think, Dr. Boyd, that a

great many of our examinations are in many instances routine. There is very little history or symptoms that might be correlated with the diverticulum or diverticula seen roentgenographically.

I think that most (and I mean over 75 per cent) of the diverticula that we see in the duodenum are not the cause of the symptoms for which the patient was referred to us.

Dr. Boyd:—Dr. Speer, I will pass you for now.

Before I think of other questions, I will ask Dr. Glass a final question before we start taking them from the floor.

Are there any new drugs, newer agents, in the treatment of peptic ulcer, or, to put it more broadly, what gastric drugs are there that you think are of great significance?

Dr. Glass:—There are many good agents for the medical treatment of ulcer, but I think all of us would agree that we are unable to prevent relapses. We know that there are about 30 per cent relapses within one year, and up to 70 per cent relapses in two years, though there is a good response to original treatment. I believe that as yet there is no reliable medication available to prevent relapses of peptic ulcer, though some of the recent drugs such as C-88 or Robuden may extend the duration of the interval period.

It might be interesting to explore the possibility as to whether the same drugs which are used for treatment of relapses can do something to prevent the relapse if they are used ahead of time, i.e. in the asymptomatic period before the development of the relapse in the particular patient.

Several years ago, with this in mind, I started extensive treatment of the chronic ulcer, just two or three weeks ahead of the usual time when the next relapse was expected. I was rather satisfied with this procedure because I often felt that the relapse was prevented. Some of the ulcers have such a well-scheduled calendar that one can draw rather definite conclusions as to this point. I would be interested in hearing from others on this subject because as yet I am not convinced that there is any other reliable way to prevent ulcer relapses with medical treatment.

Dr. Boyd:—Dr. Speer, is there any question on pathology you wish I would ask you?

Dr. Speer:—I couldn't let pass without comment Dr. Glass' statement about his thinking that mass screening of patients would be a feasible procedure to find early gastric carcinoma. I don't know exactly what the figures in the gastric screens are, but I am sure when they are finished they will turn out to be like those in screening sputum and screening the cellularity of vaginal secretions, in which it was discovered that it cost about $10,000 to find a single case. You

have a much more difficult situation by location and from limited knowledge of the biology and cytology of the early gastric cancers, we look for absolutely nothing from mass screening.

On the other hand, I would say that a patient with achlorhydria and other such symptoms, or pernicious anemia, should certainly be screened, by whatever means you wish, but these are a small and highly selected group of individuals.

Dr. Boyd:—Apparently the questions I have put to the panel have lacked something in significance or importance, but I have enough now to last us the rest of the convention.

Here is a question for Dr. Borrelli. I think he has already answered it, but I will repeat it. "What percentage of peptic ulcers may be missed in an *adequate* roentgenologic examination of the stomach and duodenum?"

Dr. Borrelli:—So far as I am concerned, very few. I was going to say none, but that would be hard to prove.

Dr. Boyd:—Dr. Colp, this question: "In gastric ulcer, how radical a subtotal gastrectomy do you advocate? Is node dissection, splenectomy, and so forth, indicated?"

Dr. Colp:—You are bringing up a very moot question here, in which I do not agree with many of my colleagues, and the fact that I do not agree with them does not necessarily mean I am wrong. (Laughter)

I think that a gastric ulcer which may be benign but has the potentialities of being malignant, is that type of gastric ulcer which should be treated by radical subtotal gastrectomy in which two- to three-quarters of the stomach is removed; the gastric artery is ligated, and the greater omentum is removed but the spleen is left intact.

My following statement may seem inconsistent. I feel that those gastric ulcers which are situated close to the region of the esophagus, and which the roentgenologist, the surgeon, and all tests point to as being benign rather than being malignant lesions—that in those cases, rather than perform a radical total or an esophageal gastrectomy, the Madelener procedure should be done, in which the distal two-thirds of the stomach is removed and the ulcer left *in situ*. Following this procedure, these ulcers will heal unless they are carcinomas.

When I indicated that I would be speaking inconsistently, I appreciate the fact that the dictum is that all ulcers should be removed for pathologic examination, but I feel as did Lord Acton that the worst use of theory is to make men insensible to fact. We have performed the Madelener procedure in 17 cases and we were wrong twice. These patients developed carcinoma. One, in the opinion of Dr. Klemperer, the pathologist, had nothing to do with the ulcer, and the other lived four years, and died of carcinoma proven by autopsy, which is not a bad follow-up even for a total gastrectomy.

Question:–What do you think of routine gastrointestinal series every year for patients over 40, for routine detection of carcinoma of the stomach?

Dr. Borrelli:–I think Dr. Speer answered that.

I would say the same thing. I think the number of radiologists are not available to do it intelligently.

Dr. Boyd:–Let me change this gentleman's question, then. How early can gastric carcinoma be determined roentgenologically in the sense of affording a reasonable chance for a surgical cure?

Dr. Borrelli:–Very rarely early enough! But that is a different problem and not radiologic.

Dr. Boyd:–Do you want to answer, Dr. Speer? Do you think routine annual gastrointestinal series would serve to greatly reduce the problem of resectable or curative cancer of the stomach?

Dr. Speer:–We wish that it would, but we don't see any hope for the roentgenologic diagnosis in time to provide cure for many individuals.

Dr. Colp:–Could I answer part of that question?

I think that brings us back to the question of gastric ulcer. I think that it is rather difficult to make a diagnosis roentgenologically between benign gastric ulcer and gastric carcinoma. Fifteen per cent of patients that we operated upon in a series of over 500, were treated by the medical men of our institution for gastric ulcer and, as a matter of fact, were treated by roentgenography. They were x-rayed regularly for their gastric ulcers, and finally these ulcers, which presumably were benign, reached the stage of inoperability.

I feel if we are to make any advance at all in the surgery of carcinoma, and certainly if these cases can be gotten before glandular metastases, patients have a 50 per cent chance of a five-year over all cure, which is something, and this is one of the chapters that I think should be emphasized, and one reason why chronic gastric ulcers should be operated upon.

Dr. Boyd:–Just a second, Dr. Colp. Supposing a patient with a gastric ulcer has medical therapy, and suppose the crater disappears, and suppose the case becomes asymptomatic–let's assume that happens–how often do you think they should be restudied to make sure that a gastric carcinoma is not lurking?

Dr. Colp:–I have seen–and so have you–cases under medical therapy in which the ulcer to all intents and purposes, as evidenced by roentgenological examination, disappears, and the patient is well, yet, on gastroscopy there was shown a residuum of an area of ulceration. In many instances where these patients have been operated upon, a carcinoma was present.

I imagine that any patient who has a gastric ulcer that is treated medically, if his roentgenologic films are negative, and if he has a gastroscopic examination —and this is one of the regions in which gastroscopy is of value—that is negative, he might go along until he had a recrudescence of his symptoms, at which time he should be x-rayed again. We know it is a recurrent chronic disease, and when you speak about surgery of gastric ulcer, you are not speaking simply about duodenal ulcer, in which you have an incidence of gastrojejunal ulceration postoperatively. That is practically nonexistent following surgery for gastric ulceration, and you can really promise the patient a cure. If a patient has a gastric ulcer, I am sure you are broadminded enough to have this man operated upon not only because of the possibility of cancer, but because surgery will offer him a cure without recurrence either at the gastrojejunal stoma or in the remainder of the stomach.

Dr. Boyd:—You started to raise your hand, Dr. Borrelli.

Dr. Borrelli:—I wanted to ask Dr. Colp whether he has not seen cases where the radiologist hardly noted any lesion, minimal to be sure, or felt it was benign, and the surgeon went in to remove it, only to have the pathologist report it as malignancy. Yet in other cases that were almost normal from every point of view, the pathologist, making a serial study, reports no malignancy, yet the patient is dead of metastases in six months or a year?

So what would be the advantage for me to find those so called "normal" cases to report on, with little or no involvement, only to have the patient operated upon in vain. If the so-called early ones are almost normal in appearance and do not do well surgically, how then can we find in a serial routine study, enough early cases to help. Furthermore, to be done well we would need two or three times as many competent radiologists and gastroenterologists as are available.

Dr. Boyd:—Dr. Colp, supposing you operated on a patient for hematemesis, and, on opening the stomach, there was blood but no actual ulcer was found, would you do a total or subtotal gastrectomy?

Dr. Colp:—That question is one that deserves very serious consideration. I think that any patient with bleeding that is not controlled, and provided esophageal varices can be ruled out, and if you operate upon the patient, as is predicated here, and this patient has bleeding from his stomach, a careful search through an adequate gastrotomy should be made of the interior of the stomach. There is one notorious place for shallow bleeding gastric ulcers, and that is high in the cardia close to the esophagus.

In this type of case, the left gastric artery should be ligated, and the area of ulceration which is bleeding may be treated with hemostatic sutures. Often following the mobilization of the stomach and the esophagus by dividing the vagi, the high ulcer may be removed by subtotal gastrectomy. Patients in whom

no definite lesion is found at the time of exploration, and upon whom you have done a subtotal gastrectomy, may very well return with bleeding from their stomach. This is one of the areas in which you may be able to do constructive research.

Dr. Boyd:—That is fair, in regard to Dr. Colp's adequacy of malignant degeneration of gastric ulcers. "Have you ever seen a gastric ulcer actually degenerate into a gastric carcinoma?"

Dr. Speer:—That is a loaded question.

I think we would have a wonderful follow-up here if we had a person who had seen a carcinoma develop from anything, anywhere, at any location. I have never seen one. We have, however, seen ulcers in which we think the carcinoma was secondary to the ulceration. These, however, I think, are rare. We would say about 0.1 per cent of the chronic gastric ulcers which we see give rise to cancer.

I think we have been talking about many things up here. One has been the treatment of chronic gastric ulcer, whether that should be medical or surgical. You can justly argue about that, but I think if you have the impression that by surgery of chronic peptic ulcer you are doing something to solve a problem of gastric cancer, you are sadly mistaken.

Dr. Boyd:—Someone wants to know if there is any difference in the incidence of atrophic gastritis as related to the degree of treatment in pernicious anemia.

Dr. Glass:—One of the errors made by some of the gastroscopists which is found in many textbooks is that gastric atrophy of pernicious anemia may subside under the effect of liver treatment. We know at the present time that it does not disappear. The biopsies obtained with suction instruments have proved that atrophy of the gastric mucosa in pernicious anemia does not disappear under the effect of treatment. This atrophic lesion in pernicious anemia is like a scar and it never subsides.

The atrophic gastritis due to different etiology may, however, disappear under any kind of treatment, or without treatment, especially if it is only partial, incomplete, or patchy.

Question:—Have you had any personal experience with the method of treatment of hematemesis with *per os* thrombin, or powdered gelfoam, with milk, to control acute duodenal hemorrhage in an elderly bad surgical risk?

Dr. Colp:—I have had no personal experience, because it has been our rule to admit bleeding ulcer cases to the medical side and transfer them subsequently to the surgical side.

I should like to answer something that Dr. Speer intimated, if I may.

Anybody who would look at my benign countenance would know I certainly wouldn't try to mislead anyone, especially gastroenterologists (laughter), but what I meant to imply is that very often in cases of ulcer it is very difficult to distinguish between an ulcer that is benign and an ulcer that is malignant. Moreover, in the work that Klein[8] and his associates did, about 3 per cent of our cases were ulcers which had undergone malignant degeneration. We also know that gastric carcinomas that ulcerate may slough out, so that they give the impression of benign ulcer. It is because of this difficulty in diagnosis that I believe if these lesions can be gotten early, especially the ulcer type, that the end result will be better, and I hope Dr. Speer understands what I mean.

Dr. Boyd:—You understand, Dr. Speer, and I will pass on to the next question. (Laughter)

Dr. Speer:—Well, of course, I mean, I understand, and Dr. Colp is right about the difficulty of making the diagnosis clinically or with x-ray study, but I still think the problem of finding a cure for gastric carcinoma is a difficult one. Dr. Ackerman, in Chicago, speaking on this, said he was afraid that most surgeons had had the Jehovah complex when they approached the problem of cure of the ulcerating carcinoma vs. the chronic peptic ulcer.

Dr. Boyd:—I pass this question for both Dr. Glass and Dr. Colp: "In a case where there are simultaneous gastric and duodenal ulcers, would you consider the patient had some ulcerative disease, broadly speaking, and would you treat such a case surgically or medically?"

Dr. Glass:—Well, I think nobody believes anymore in this old concept of ulcerative disease. On the contrary, there is some recent evidence which indicates that gastric ulcer and duodenal ulcer are etiologically different diseases. All of you probably heard about the new concept of Dragstedt, that duodenal ulcer is due to the excessive central vagal stimulation of gastric secretion, but that gastric ulcer forms on the basis of an increased amount of hormonal stimuli, i.e. increased formation of gastrin in the stomach. If this is true, in this particular case we would have to say that both mechanisms were active, which is probably not right.

There are also some other reasons for feeling that gastric and duodenal ulcer are not the same diseases. Especially interesting in this regard is the histology of the mucosa in the adjacent area to the ulcer. You know that in gastric ulcer there are usually extensive atrophic lesions around the ulcerative lesion. On the contrary, in duodenal ulcer there is hardly any pathological abnormality in the gastric mucosa. The so-called hypertrophic gastritis associated with duodenal ulcer turned out to be a myth when scrutinized by gastric biopsy technic. This again indicates different mechanisms of both diseases. Benign gastric ulcer might be due either to some localized defect in the continuity of the mucus lining of the stomach which forms a soft spot of the

mucosa, or it might arise from some localized erosive lesion, or be due to some inflammatory process in the stomach. Duodenal ulcer, on the other hand, is certainly associated with gastric hypersecretion and hypermotility, broadly speaking, gastric hyperfunction.

Fortunately, both types of ulcer respond to the same medical treatment if they are benign. I would try, therefore, to treat this case medically, but I would be very suspicious of the nature of the gastric ulcer. If the gastric secretory study would show low acidity and low output of other glandular components, I would be rather suspicious of the nature of the gastric ulcer, and if a few weeks of treatment would not give complete clinical recovery I would not wait more than four weeks, and would decide on surgery.

Dr. Colp:—I think Dr. Glass' answer was very thorough and no second comment is needed.

Question:—Under what conditions would you advocate surgery for duodenal diverticulum?

Dr. Colp:—I think in the majority of patients with duodenal diverticula they have very few symptoms which would be directly attributed to that particular lesion. If the diverticulum was on the anterior wall, it might be removed, but many of these diverticula are on the posterior wall, and in many of them the ducts open into the diverticulum, so we have been in the habit of side-tracking these diverticula by doing a subtotal gastrectomy. The results have been no worse than in those cases where an attempt was made to remove them, and in many cases, whether because of the operation or in spite of it, these patients have been improved.

Dr. Boyd:—Dr. Colp, again, supposing a patient had had a subtotal gastrectomy which seemed adequate, and following that, had terrible hemorrhaging, and no gastric or jejunal ulcer is demonstrable, do you think vagotomy would be an ample added procedure?

Dr. Colp:—I think if the patient has had an adequate subtotal gastrectomy and has hemorrhages, that the addition of an intradiaphragmatic vagotomy might help, although at that stage of the game, when you do it, these patients may subsequently hemorrhage, but I think we should take a lesson from the recent finding of Zollinger in a case like this.

The pancreas, which can easily be seen with removal of the stomach, should be carefully examined for the presence of adenomata. We all know now that cases of recurrent ulceration might be due to the adenomata of the pancreas.

Dr. Boyd:—Dr. Glass, I think this is the final question: "What percentage of patients with gastric carcinoma do not have a histamine resistant anacidity?"

Dr. Glass:—Some 30 to 33 per cent, approximately. In a very extensive study of LaDue and Pack, in about one-third of the cases of gastric cancer free HCl

was present in the stomach. In association with Drs. Wolf, McNeer and Bowden, we found that other glandular secretory products of the stomach, such as pepsin, and glandular mucoprotein are also present in gastric juice in about one-third of the cases of gastric cancer. The percentage is similar therefore to that of hydrochloric acid, which means that one-third of the cases of gastric cancer are not associated with complete atrophy of the gastric mucosa.

Dr. Boyd:—I will ask one more, Dr. Borrelli, and then you can close this, Dr. Borrelli, if you will.

"Does the history of the internist, and do the physical findings of the internist help or hinder your interpretation of x-ray findings, and does the presence of the internist help or hinder you in making the diagnosis?" (Laughter)

Dr. Borrelli:—In our department we demand a history. We don't get it from the attending very often, so we have to send the resident or intern for it. Yes, we feel that the history helps us tremendously, but the history will never find the lesion that is not demonstrable on the x-ray film. We must first find some disturbance or changes in the stomach and only then can we try to make a differential diagnosis. That does not mean differentiation between an ulcer and a carcinoma, because I think that is very, very difficult. I believe too many internists use their history and physical to "see" the x-ray findings that are not present. Very often the presence of the internists is a hindrance.

Dr. Boyd:—I want to thank the members of the panel for their cooperation, and the audience for their attention. I hope something interesting and instructive has been said this afternoon; I thank all of you.

HISTOPLASMOSIS AND THE GASTROENTEROLOGIST*

DONALD C. COLLINS, M.D., M.S. (Path. & Surg.), F.A.C.G.†
Hollywood, Calif.

Gastroenterologists must familiarize themselves with a relatively new American disease that has only received general recognition in the past five years, namely histoplasmosis. Darling[8] first described this disease just 50 years ago, while working as the pathologist at the Ancon (now Gorgas) Hospital in the Panama Canal Zone. He correctly identified the specific causative organism, but mistook it for a protozoa, naming it *Histoplasma capsulatum*. Darling's original three patients died. In the early portion of this century, the world's medical literature contained an occasional sporadic fatal case-report, emanating chiefly from the tropical Americas.

The first case-report (fatal) of this disease to be reported[21] from the United States, occurred in Minnesota, in 1926. De Monbreun[16] (Vanderbilt University School of Medicine), in 1932, demonstrated the true fungus origin of histoplasmosis and proved that the life cycle of the *Histoplasma capsulatum* could only be completed by passing the "mycelial-form" through intermediate animal hosts, such as: the dog, cow, horse, etc. By 1945[18] only 71 cases had been reported, almost all coming from the United States. By this date the concept of a tropical disease had been abandoned and it was being realized for the first time that histoplasmosis did exist in this country in a predominately benign form and that most patients recovered without any specific form of therapy being used. By 1951[13], only 138 authenticated instances of histoplasmosis had appeared in the world's medical literature. Eighty per cent of these cases originated within 24 states of this country. Forty-three per cent were correctly diagnosed during life. Rapid strides have been made in the past five years in the United States in improving methods of correct diagnosis and the earlier recognition of instances of histoplasmosis.

The reader is referred to the earlier contributions by this author[1-7] for a detailed review of histoplasmosis and its behavior in the human. Suffice it to say, in passing, that evidence has been presented that this organism is the probable principal cause of juvenile mesenteric lymphadenitis[2]; that it has a general incidence of approximately 12 per cent among the general population of Southern California[5,14], that nearly one-third of the examples of both "nonspecific regional enteritis of the small intestine" and "chronic ulcerative colitis" exhibit specific "positive" histologic evidence of the presence of the *Histoplasma capsulatum* in the surgically excised fresh tissues[4], and that this bizarre disease

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†Assistant Professor of Surgery, College of Medical-Evangelists, Los Angeles, Calif.

chiefly affects the young. In a previous communication[3], I pointed out that this specific fungus had been found histologically in at least 7.8 per cent of a consecutive unselected series of 50,000 specimens of the human vermiform appendix. More recently[4], an incidence of 13.6 per cent was found in 1,205 surgically excised, fresh, colonic tissue specimens, but that this figure was decreased to 8.3 per cent, if the 179 instances of "chronic ulcerative colitis" were excluded from consideration. Recently a study[6] detailed my study of this fungus in 1,542 coloproctologic surgically excised fresh specimens. This research represented three years' intensive laboratory study, employing elaborate and complicated culture technics. In 801 instances (51.7 per cent) it was found that the accuracy of the histological "positive" tissue diagnoses, using either the Hotchkiss-McManus modification or the Kligman-Mescon[19] modification of Schiff's periodic acid stain, was substantiated in 91.6 per cent of cases by means of elaborate month-long bacteriologic culture technics[6], costing many thousands of dollars.

From this recent and continuing study it appears reasonable to suggest that in the future, greater reliance may be placed on the diagnostic accuracy of these specific tissue staining technics and also upon the specificity of the "starry-sky" phenomena, originally described by Raftery[20], in 1951, working at The Henry Ford Hospital in Detroit. It may now be stated unequivocally that the histologic finding of the "starry-sky" reaction in the "germinal centers" of diseased lymph nodes of the gastrointestinal tract is every bit as reliable and diagnostic for the presence of histoplasmosis; as is the reliance that all of us have in promptly diagnosing the presence of a myobacterium tuberculosis infection in the presence of a typical tubercle formation in human tissues.

Histoplasmosis is primarily a disease of the young and in those up to the age of 40 years. The aged[7] exhibit only the late residuals and complications resulting from acquiring this disease in their earlier years of life. It is believed that man receives his initial infection from breathing into the lungs[11,15,17,19,22,24] dusts contaminated by the "mycelial-form" of this fungus, after it has passed through the gastrointestinal tract of man's most common animal companions, namely: the dog[9], cat, horse, cow or steer, and chickens[12]. Their droppings contaminate the soil over which man walks and breathes. A human, nonfatal epidemic of histoplasmosis was described in 1955[12], occurring in one family, which originated from the chickens of one hen coop on their farm. Not only were all five humans of this family severely infected, but also were the rest of the animals on that particular farm. A similar human epidemic was detailed[23] from Wright County, Minnesota in 1955, that infected eight members of one family, with some deaths.

The initial infection in the human usually occurs in the lungs. There a mild bronchopneumonitis may ensue, that usually subsides after several weeks of symptomatic general supportative measures. During the course of the pneumonitis, the lesions often ulcerate and the specific organism is carried by the blood

stream to the gastrointestinal tract, where it finds conditions more suitable for its continued propagation and survival. In the lungs, the late residuals of this disease are characterized by extensive calcifying or calcified, small, widely disseminated parenchymal nodules, in an entirely different distribution pattern from that observed in pulmonary tuberculosis[10]. In this pathologic entity, usually the apices are spared and the predominant concentration of calcification is not localized to the hilar lymph nodes. Rarely, we may encounter, as a late sequela, a localized lung abscess-like lesion caused by histoplasmosis. Such localized lesions are dramatically cured by a lobectomy[13,19,24]. The same "bird-shot" calcified nodular appearance is commonly noted throughout the splenic parenchyma and it is believed to be highly suggestive of the presence of histoplasmosis. There is far less late parenchymal calcification observed throughout the liver.

TABLE I

INCIDENCE OF HISTOPLASMOSIS IN THE GASTROINTESTINAL TRACT

Source of Material:	Total Number of Specimens:	Proven Histoplasmosis:	
		Number of Cases:	Per Cent of Material:
Juvenile Mesenteric Lymph Adenitis:	151	78	52.6
Nonspecific Regional Enteritis:	219	69	31.5
Vermiform Appendix:	50,000	3,905	7.8
"Chronic Ulcerative Colitis":	179	64	35.7
Colon, Minus:—"C.U.C.":	1,026	100	9.8
Anal-Rectal Region:	1,542	177	11.5
Grand totals:	53,117	4,393	8.3

Following the escape of the *Histoplasma capsulatum* from the lungs into the blood stream, there is a transient hepato- and splenomegaly. The most serious late stigmata and complications of histoplasmosis are to be found in the gastrointestinal tract. The finding of clusters of calcified ileal mesenteric lymph nodes is now generally accepted as presumptive evidence of a previous attack of juvenile mesenteric lymphadenitis, where tuberculosis has been excluded. In a previous study[2], it was fairly well substantiated in a group of patients who were rechecked 20 years after their abdominal cavities had been surgically opened and a diagnosis of juvenile mesenteric lymphadenitis proven[1]; now had a high percentage of "positive" evidence of the existence of histoplasmosis, such as: chest roentgenograms positive for histoplasmosis (83.3 per cent), positive histoplasmin skin tests (62.5 per cent), and a small number (12.5 per cent) of still active positive complement fixation tests. New microscopic tissue sections, taken from these appendices and regional ileal mesenteric lymph nodes and stained by the specific Hotchkiss-McManus modification of Schiff's periodic acid

stain, showed a high percentage (61.0 per cent) of "positive" histologic evidence of the presence of the *Histoplasma capsulatum*.

In 179 examples of "chronic ulcerative colitis" and in 219 cases of "nonspecific regional enteritis"[4], the "positive" histologic evidence of the presence of histoplasmosis was three times that of other similar regional tissues from the same intestinal area which were surgically resected for a variety of reasons. This triplication of incidence appears to be significant, although it is readily admitted that this small number of patients is insufficient from which to draw, at the present time, any specific or dogmatic conclusions as to the possible relationship of this unusual fungus to these two poorly understood intestinal disease entities.

In a series of 1,542 consecutive unselected anal-rectal patients, where tissues were excised, an average incidence of histoplasmosis was found to be 11.48 per cent. This incidence was increased in 49 rectal ulcers to 18.37 per cent, and in anal ulcers and fissures to 13.88 per cent. In a study of 176 rectal polyps, this incidence percentage was 18.09.

Further work should be done along these lines of study to determine if these incidence statistics possess any significant value in the final analysis. Most patients acquire these two intestinal diseases in their younger years. Often, as gastroenterologists we are left to treat the late residuals of: fibrosis, extensive scarring, loss of normal motor function, pseudopolyp formation, deep ulceration, varying degrees of bowel obstruction, fistulae, loss of normal physiologic digestive functions, diarrhea alternating with constipation, and rarely engrafted malignant changes. Often, the only possible solution to this Gorgonian knot is to employ the classical Alexandrian-method of complete surgical excision of the diseased tissues; if we desire to restore our patients to reasonable health and to increase their longevity.

Table I summarizes the incidence of histoplasmosis in 53,117 specimens derived from various regions of the gastrointestinal tract. It is believed that these data are self-explanatory and need no further elaboration.

Conclusions

1. All gastroenterologists should familiarize themselves with a common, but largely overlooked American disease, namely: "histoplasmosis".

2. Histoplasmosis is endemically distributed throughout the warm, moist areas of the United States.

3. The average incidence of this disease varies from 70-90 per cent[18] in the Mississippi Valley west of the Appalachian foothills to about 12 per cent in the Southern California Region[5,14].

4. It appears probable that juvenile mesenteric lymphadenitis, "nonspecific regional enteritis of the small intestine", and "chronic ulcerative colitis" may be

indicative of varying tissue reactions of the infected human to histoplasmosis, depending upon his resistance and the initial dose of the infection.

5. The *Histoplasma capsulatum* is a member of the *fungi imperfecti*. Man can apparently only become infected by the "mycelial-form" of this fungus, after it has developed within the gastrointestinal tract of the intermediate host, namely: the dog, cat, horse, cow, chicken, etc.; all of man's closest animal friends. Man only exhibits the "yeast-form" of this organism within his tissues. Apparently, one man can not directly infect another man.

6. Human histoplasmosis usually begins in the young by breathing in contaminated dust into the lungs; where a pseudocaseous, specific parenchymal lesion develops. The blood stream carries the organisms from the initial focus in the lungs to the liver, spleen, reticuloendothelial system and the gastrointestinal tract.

7. In gastroenterology we are usually concerned with the late stigmata and complications of histoplasmosis, as they affect the gastrointestinal tract.

8. In a study of 53,117 various specimens from the gastrointestinal tract, 8.27 per cent of these specimens exhibited "positive" evidence of histoplasmosis. In instances of mesenteric lymphadenitis of juveniles, "nonspecific regional enteritis of the small intestine", and "chronic ulcerative colitis" this average incidence was increased by more than 400 per cent.

9. The treatment of histoplasmosis is still largely symptomatic, although recent studies indicate that Atabrine R may possess great future value. Ethyl vanillate[17], methyl testosterone and sulfonamides, promin and the trivalent or pentavalent forms of antimony[22] have been recommended as possessing therapeutic value.

10. The "starry-sky" of histoplasmosis is just as diagnostic of this disease as is the histologic appearance of the typical tubercule of human Myobacterium tuberculosis infections.

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Discussion

Dr. Fred E. Manulis (Palm Beach, Fla.):—Dr. Collins is to be congratulated for his most comprehensive and provocative presentation here this morning. He has devoted much time and effort in his studies, which have been motivated by enthusiasm and sincere dedication.

The conclusions he has drawn on the incidence of "proven" histoplasmosis in the gastrointestinal tract; namely: 52.6 per cent of 151 cases of juvenile mesenteric lymphadenitis; 31.5 per cent of 219 cases of nonspecific regional enteritis; 7.8 per cent of 50,000 cases where the vermiform appendix was removed; and 35.7 per cent of 179 cases of chronic ulcerative colitis, are quite controversial and are postulated upon certain criteria for diagnosis; namely, the histologic demonstration of the "starry sky" phenomenon, without confirmation by culture of the organism *Histoplasma capsulatum.*

I should like to confine my remarks to criteria for diagnosis, since it is in this sphere where the controversy exists.

Since the etiology of this protean disease, histoplasmosis, is known to be caused by tissue invasion of the fungus *Histoplasma capsulatum*, it is reasonable to conclude that an unequivocal diagnosis must be based on the demonstration of the organism by cultural methods. All other methods must be considered, at best, indirect evidence. These are histoplasmin skin test, complement fixation, and histologic examination of biopsy material.

The histoplasmin skin test, when positive, can mean either past or present infection. A negative reaction does not necessarily rule out infection, since it is frequently negative in culturally proven cases, especially those severely ill with the disease.

Results with the complement fixation test have not been too satisfactory. A positive reaction with a high or rising titer usually indicates active or progressive disease, but cross-reactions with other diseases such as blastomycosis or coccidiodomycosis have been known to occur. A low titer or negative reaction does not rule out active disease.

We now come to the tissue response to the invasion of the fungus *Histoplasmus capsulatum*. Three types of reaction have been observed:

1. Isolated organisms in phagocytic cells with minimal or no tissue reaction.

2. Marked histiocytic proliferation with phagocytes containing many spherical or oval encapsulated organisms 2 to 5 microns in diameter.

3. A granulomatous form either of the productive (tubercle) or the exudative (caseating) variety.

Any or all combinations of the above may exist.

Whether one can state unequivocally, as Dr. Collins has done, that the histologic finding of the "starry-sky" reaction in the germinal centers of diseased lymph nodes of the gastrointestinal tract is reliable and diagnostic for the presence of histoplasmosis, is open to question. The cellular reaction *per se* is a nonspecific one and found in many other disease states. The morphologic diagnosis of *Histoplasma capsulatum* in tissue may be very difficult at times, even in the hands of the most experienced observers.

The only other observer in the literature with comparable diagnostic criteria and results, is Alan Raftery, in the *Journal of the American Medical Association*, 27 January 1951, quoted by Dr. Collins, who studied 436 appendices, comprising all cases of chronic appendicitis, lymphoid hyperplasia of the appendix, and normal appendixes in children 16 years of age and under, submitted in a ten-year period at the Henry Ford Hospital. Fifty-four of these were found to contain *Histoplasma capsulatum*. Only one positive culture on artificial

medium was obtained. The remainder of the cases were diagnosed on morphological demonstration of the "starry-sky" pattern of reactive hyperplasia and numerous yeast-laden macrophages.

Dr. Hobart Reimann, of Philadelphia, commenting on Raftery's findings, stated "granules such as Raftery described were occasionally found, but we have not considered them to be histoplasma morphologically."

Dr. Edwin Hirsch, of Chicago, also commented: "I raise the question about the character of the inclusions, as Dr. Reimann did. It seems to me that more evidence of the character of the inclusions and that they are actually *Histoplasma capsulatum* are needed".

In contrast, one might note the results of the experience of this disease at the Mayo Clinic, reported by Vivian, Weed, et al, in *Surgery, Gynecology and Obstetrics*, July 1954, where the diagnosis of histoplasmosis was made in only 20 cases. The diagnosis was proved by culture in 19 cases. Only one case was accepted, because "the pathologic and clinical picture was consistent with that of histoplasmosis, and the organisms seen on microscopic section were typical *Histoplasma capsulatum*".

In closing, I feel that we are all indebted to Dr. Collins for stimulating our interest in a disease which most of us rarely think of, and should consider in our daily diagnostic ventures.

Dr. Donald C. Collins (Hollywood, Calif.):—Dr. Manulis, I think, possibly failed to read the third page of the copy of the manuscript I sent him; and I quote:—

"Recently a study detailed my study of this fungus in 1,542 coloproctologic surgically excised fresh specimens. This research represented three years intensive laboratory study, employing elaborate and complicated culture technics. In 801 instances, 51.7 per cent, it was found that the accuracy of the histological 'positive' tissue diagnoses, using either the Hotchkiss-McManus modification or the Kligman-Mescon modification of Schiff's periodic acid stain, was substantiated in 91.6 per cent of the cases by means of elaborate month-long bacteriologic culture technics, costing many thousands of dollars".

Now, in regard to the Mayo Clinic, I was a Fellow in Pathology there myself, and 20,000 of these appendices come from that clinic. I showed some of these appendices to Dr. Albert Broders, and he had missed the *Histoplasma capsulata*. I had failed to recognize them. We had all missed this fungus. Our hospital pathologists back in Los Angeles overlooked these lesions. When you can take specific tissues, culture them, and bring out a 91 per cent agreement between your histological diagnoses and your culture technics, I think it is a little bit more than just a coincidence.

THE PRESENT MANAGEMENT OF ULCERATIVE COLITIS WITH SPECIAL EMPHASIS ON SPRUE DIET*

HENRY A. MONAT, M.D., F.A.C.P., F.A.C.G.
Washington, D.C.

The paper I am about to present embraces an internist's viewpoint. I may be accused by the surgeons of being too conservative, but I feel we have reached a crossroad in the treatment of ulcerative colitis and that we have to outline a blueprint upon which we may decide which road to follow: the surgical one or the medical one. I do not envy any doctor who is called upon to handle this disease. He is constantly frustrated, is in a continual state of emotional tension and many times, just when he is about to reach a radical decision, to his pleasant surprise, the disease may turn favorably and a remission set in. For the simplification of the treatment, I have divided these patients into three types.

Type A:—This type of ulcerative colitis is usually simple and uncomplicated. It starts with some rectal bleeding. Stools are usually formed. There are no symptoms. These patients are frequently mistaken for having bleeding hemorrhoids. If not treated, the bleeding continues and the patient begins to have frequent stools and may run a low fever. After a while he may start having tenesmus and uncontrolled bowel movements. He also begins to become more agitated. The barium enema at this point is negative. The proctoscopic exam reveals friability and traumatic mucosa. These cases are the most hopeful ones to treat from a medical standpoint. The patient is told *firmly* that he has ulcerative colitis, the seriousness of it, that it requires painstaking cooperation on his part in following a dietary and *modus vivendi* routine. He is told not to expect complete clearing of his symptoms under six months, not to be discouraged by occasional exacerbations, and the prognosis is good. For this type of ulcerative colitis we give:

1. Chemical treatment consisting of Chlorstrep. 500 mg. every 8 hrs. for 4 days with sulfathalidine 15 gr. q. 6 hrs. for 14 days. Two weeks rest and the procedure is repeated again. At the end of this time of treatment, symptomatic and proctoscopic appraisal is required as to whether the antibiotic and sulfa are to be continued.

2. Emotional treatment consisting of thorazine 25 mg. t.i.d. ac and pari passu Reserpine .25 mg. b.i.d. morning and bedtime. Thorazine is given for a week and Reserpine is continued for six months.

3. Dietary treatment—before detailing the diet, permit me to preface it by stating that for the past 8 years I have applied this sprue diet in various

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types of ulcerative colitis with universal and dramatic success. This diet, in my hands, had rapidly diminished the number of bowel movements and bleeding. The strictness of this diet and the difficulty of adhering to it should be emphasized to the patient and he should be told that unless he follows it religiously, there is no hope for him.

At the beginning of the treatment, the patient is placed on a basic regimen consisting of:

Breakfast: pot cheese, bananas, protein milk

Lunch: ground-up lean meat (veal, chicken, beef), pot cheese, bananas, protein milk.

Dinner: the same as lunch. A tablespoon of Knox's gelatin can be added to a glass of protein milk with each meal.

After one week and on improvement, warm orange juice with Knox's gelatin and eggs are added.

After two weeks and further improvement, meaning solidification of stools, diminution of number of bowel movements and lessening of bleeding, pureed vegetables are added one at a time. Supposedly after addition of spinach frequency of stools increase, then this vegetable is withdrawn and another one is introduced, such as pureed carrots.

To reiterate, the principle of sprue diet consists of no other carbohydrates except the ones found in fruit and to a lesser degree in vegetables, and in protein milk. Cereals, including corn, wheat, rye or rice in any form are strictly forbidden. Potato is prohibited. Milk, other than protein or calcium caseinate milk, is not allowed. All foods must be completely pureed and mashed, and partaken in small quantities (to minimize gastrocolic reflex); neither cold nor too hot. It is our belief that even the minimum roughage is detrimental to colonic mucosa for many months. Only after six months, regular milk and other carbohydrates such as bread or potatos can be gradually reintroduced. Fruit juices and honey, being fructoses, can be used from the start. In addition to the diet, patient receives daily for at least 60 days intramuscularly 100 mg. of B_1, 100 mcg. of B_{12}, 500 mg. of Vitamin C. Per os, he receives 4 tablespoons of Gerval protein powder and six CVP ascorbic acid tablets.

Type B:—This type of case starts with great vehemence. Patient has 12 or more bloody mucoid stools, tenesmus, abdominal cramping, sharp abdominal pains, temperature up to 104°, prostration. This type may not recover and die exsanguinated unless expert and prompt diagnostic and therapeutic procedures are instituted. The following emergency measures should be started: Daily 500 c.c. of full blood followed by 1,000 c.c. of 10 per cent invert sugar solution in normal saline to which two ampules of SoluB with 500 mg. of C are added, plus 75 mg. of Vitamin K. Nothing by mouth for 72 hours or until diarrhea

abates, then proceed with sprue diet. In addition to the transfusions, give also daily 1,000 c.c. of protein hydrolysate with similar stipulations as the transfusions of blood. By hypo, 100 mg. of Achromycin every 6 hrs. and 25-50 mg. of Promazine q. 6 hrs. hypodermically. Locally, moist poultices to abdomen are given. After the temperature abates and diarrhea quiets, proceed with regimen outlined for Type A.

Type C:—This type of ulcerative colitis patient, in our blueprint, is one that has remissions and exacerbations over a period of years; is never quite normal. She may also have complications such as acute polyarthritis or rectovaginal or rectoinguinal or vesical fistulae. This is the type that usually ends up with the surgeon. Medically, it is a pity that the patient has gotten that way because with each exacerbation of this disease, the colon becomes more damaged and predisposed to malignant changes. Even if remission is accomplished, polyps are encountered proctoscopically very commonly. The treatment for these cases is to place them on a regimen outlined under Type A; if joints are involved inject them with hydrocortisone daily until improvement ensues. Give by mouth 5 mg. Meticortelone every 6 hrs. until there are no pains in the joints. Start physiotherapy for the joints. In cases of fistulae, establish scrupulous rectal hygiene and wait for surgical intervention until the patient is well (proctoscopically and roentgenologically).

The third type of patient with arthritic involvement, is the only type in which I use cortisone. In my experience, cortisone gives a momentary relief with a redoubled exacerbation when withdrawn. I use Meticortelone just long enough to abate arthritic symptoms and no longer.

Also, this group of patients has to be under frequent medical supervision, proctoscoped at least once in 3 months and re-x-rayed every 6 months. Any roentgenological change from previous x-rays, such as thickening or narrowing of the colon should be looked at with suspicion and surgical intervention contemplated. I do not subscribe to the idea that it is the best to do an ileostomy with colectomy on all of these cases. True, the chance for malignant degeneration is great in chronic ulcerative colitis with frequent remissions and roentgenological changes, but I also know that a great psychological and physiological problem is presented by a patient with ileostomy.

I may be accused of taking unnecessary chances with patients of this kind, to which I can only reply that in digestive disorders which are subject to malignant changes, one has to take a risk anyhow; I do not believe in preventative colectomies.

In conclusion, let me state that cases of ulcerative colitis lasting less than 5 years are usually medical problems and after 5 years, they become both medical and surgical ones with a strong possibility of having colectomy with ileostomy. The internist and surgeon in the latter cases must work as a team.

Summary

The ulcerative colitis cases were divided into three types and management of each type was discussed. The beneficial effect of sprue diet was emphasized. The types which should have strictly medical management were outlined and when surgical intervention should take place.

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Discussion

Dr. Jacob J. Weinstein (Washington, D. C.):—I have enjoyed reading Dr. Monat's paper and have enjoyed even more his charming and enthusiastic presentation this afternoon. He has indeed simplified the management of ulcerative colitis, and by following his "blueprint", one can easily select those cases requiring medical treatment and those which will eventually require surgical care.

Ulcerative colitis was first described by Sir William Welks, in 1875, and little has been added since to our knowledge of its etiology. No form of medical therapy has proven itself to date to be consistently effective in its cure.

Review of the natural history of ulcerative colitis indicates that it is a nonspecific, local or generalized, systemic disease subject to acute and subacute exacerbations and to frequent and unpredictable remissions.

In "Type A" of Dr. Monat's blueprint, or the mild, simple, uncomplicated form, guided medical care produces early and excellent results with long periods of recovery between bouts of recurrences. There is no dispute on how to manage this group of patients. They are strictly medical problems.

It is with this group of patients that Dr. Monat has obtained the best results with sprue diet. I do not clearly understand why a diet free of all carbohydrates except those in fruits and vegetables, and one which is free of wheat, corn, rice, potato, and milk, is superior to a palatable diet high in calories, carbohydrates and proteins, low in residue, with adequate vitamins and minerals, and free of allergenic or irritating foods.

Not too long ago I saw a young 19-year old male in the hospital showing the classical symptoms of an acute exacerbation of a chronic ulcerative colitis—eight to ten stools a day, bloody discharge, moderate febrile response, and acute arthritis of both knee joints. He was placed on the sprue diet, antibiotics and vitamins, the program described by Dr. Monat, and within six days the diarrhea had practically ceased, the temperature returned to normal, the arthritic symptoms had decreased, and the sick patient was now cheerful and clinically on the road to recovery. On proctoscopic examination some three months after the described therapy, the patient showed the typical appearance of healing chronic ulcerative colitis with pseudopolyps.

Dr. Monat has described many such spectacular results to me. Indeed, further use of this diet with more accurate clinical and laboratory studies is warranted.

Up to this point I have agreed with Dr. Monat's blueprint for the management of cases with ulcerative colitis. When, however, I review his "Type B," the case with vehement acute ulcerative colitis, and his "Type C," the case with chronic colitis of long-standing duration, with extensive disease, I am afraid that my teaching, experience, and regard for the frequent complications (50 per cent) of this destructive disease, dictate a less conservative approach than that of my fellow colleague.

In a group of 2,000 patients with chronic ulcerative colitis seen at the Mayo Clinic, 47.5 per cent had complications. Early major complications, such as perirectal abscess, arthritis, rectal hemorrhage, and cutaneous lesions, were noted in 17.5 per cent, and late major complications such as polyposis, stricture of the colon, malignancy, and perforation, in 40.2 per cent. Also it has been found that the death rate from carcinoma of the large bowel is 30 times greater in those with colitis than in the general population of the same age and sex.

The great controversies which have existed and which still exist among gastroenterologists and surgeons, are mainly due to the differences of opinion on the management of the complications, and the different ideas as to the frequency of serious or fatal complications.

The problem of whether to operate and when to operate is a difficult one, but much less difficult if one is aware of the frequency of major complications and their significance, and the fact that surgical mortality for ileostomy and colectomy is in the neighborhood of 3 to 5 per cent today as compared with 20 to 25 per cent some 20 years ago.

Just recently I really "sweated it out" working with a case of an acute exacerbation of a chronic ulcerative colitis of one year's duration in a young female, four months pregnant. She showed little response to an active medical program of three weeks' duration, and developed numerous perforations of the colon. Along with surgical intervention, the fluid, electrolyte and nutritional management of this patient demanded a most intensive amount of cooperation and team work of internist, surgeon, resident and nursing staffs.

When I left the hospital to come to this meeting, I told the residents at the George Washington University Hospital that from now on I was going to advocate ileostomy and colectomy a lot sooner in patients with chronic ulcerative colitis with recurrent attacks, than I had in the past, much in keeping with the opinions of Miller and Ripstein.

In conclusion, more definitive work on the value of the sprue diet in the medical management of ulcerative colitis is strongly indicated and should be pursued.

Ulcerative colitis is a medical disease, and surgery should be reserved for its complications. Unnecessary chances, however, should not be taken with patients with chronic ulcerative colitis. The patient should be given the benefit of early surgical treatment.

"Ileostomy and colectomy is the calculated substitution of a lesser disability for a greater."

Dr. Henry A. Monat (Washington, D. C.):—Dr. Shaiken asked me if I would consent to answer some of the questions. Before I do so, I want to answer my colleague, Dr. Weinstein.

We hope that this will be pursued, and when we get back to Washington, we may outline a research program to see why the sprue diet helps. We know that ulcerative colitis has never been reproduced in an animal. Bargen and others tried it, and made injections, but actually it was never reproduced in an animal.

We know there are so many theories about ulcerative colitis, among them the most commonly thought of, the bacterial theory, and then, of course, our psychiatric colleagues think it is blasphemy to treat them except by psychotherapy. There is this gamut of problems—we can go on and on, but I am going to relate certain opinions that have been voiced.

We had a gastroenterological dinner in Washington, and I asked all of those present to give me their opinions as to how many cases of cancer complications they saw in their cases of ulcerative colitis. I really was amazed how few there were, because I must say, I have seen a lot of ulcerative colitis in my gastroenterological years and, of course, I saw cancers, but I still saw severe cases which remained alive after years without any complications such as cancer.

I remarked in my speech that whenever they have remissions, they should be under close observation by both the surgeon and the medical man. They have to be under the observation of both. They have to be x-rayed every six months and proctoscoped every three months, and their symptoms, however trivial they may be, must be noted.

So I believe conservatism is to be advised, based upon my experience, and I still feel that it is easier to treat a person with a colon than one with a colectomy, and ileostomy. It is a terrific psychological problem.

GLUTAMIC ACID IN THE TREATMENT OF HEPATIC COMA AND ITS RELATIONSHIP TO BLOOD AMMONIA LEVELS*

NATHAN W. CHAIKIN, M.D., F.A.C.P., F.A.C.G.†

and

MAX S. KONIGSBERG, M.D.‡

New York, N. Y.

Numerous reports have appeared in the literature suggesting that hepatic encephalopathies are associated with disturbance of ammonium metabolism[1,2]. The possible relationship of ammonia derived from the catabolism of proteins to the mental symptoms in patients with liver disease has long been suspected. Van Caulaert[3] showed that the administration of ammonium salts or urea in amounts tolerated by normal individuals caused typical hepatic coma in patients with Laennec's cirrhosis. Kirk[4], after prolonged investigations, concluded that patients with cirrhosis of the liver were unable to adequately clear ammonia from the blood. Phillips et al[5] showed the deleterious effect of urea and ammonia on the mental state of patients with cirrhosis. Sherlock's group[6] showed a relationship between blood ammonium levels and the symptoms of coma. Schwartz and his co-workers[1] found that the blood ammonia values in severe liver disease were elevated with the range up to seven times that of normal. Their conclusion was that even though there was no consistent correlation between the degree of consciousness and the blood ammonia, still, the blood or plasma ammonia correlated better with the clinical status than any other available chemical determination.

The actual relationship of ammonia to the pathogenesis of hepatic encephalopathy is still controversial. While it is the concensus of opinion that protein and its derivatives can initiate or exacerbate coma in patients with severe liver damage, other substances have been implicated as possible causative agents. Sherlock's work[6] showed that methionine seemed to precipitate coma more effectively than ammonium salts or other amino acids, and that the sulfhydryl compounds were elevated in hepatic coma. These, however, are not invariably present in coma. On the other hand, Phillips et al[5], Gabuzda et al[7] showed that ammonium cation resins, ammonium chloride, as well as increased dietary protein, all produced the syndrome of impending coma.

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From the Department of Medicine, New York Medical College, Metropolitan Medical Center.

†Associate Professor of Clinical Medicine, New York Medical College. Associate Visiting Physician, Flower and Fifth Avenue Hospitals. Visiting Physician, Metropolitan and Bird S. Coler Memorial Hospitals.

‡Associate Visiting Physician, Metropolitan Hospital.

It is true that the biochemical abnormalities in hepatic encephalopathies are not specific, but one is impressed with the high blood ammonia levels which one encounters in practically every case. No other biochemical change seems to correlate as well with the clinical picture as does the plasma ammonium determination, despite the fact that this correlation is not absolute. It must be kept in mind that muscle tissue can remove up to 50 per cent of the blood ammonia coming to it. Thus the venous blood values do not necessarily mirror the ammonia content of the arterial blood. This is especially true in those cases which may show moderately increased ammonia levels over long periods of time without coma, and which then gradually lapse into coma. This has been attributed to the disturbance of the oxydative process in the Krebs cycle by the moderately and chronically increased ammonia in the plasma. Thus it is at times possible to encounter a case of hepatic coma with only moderate increase in the blood ammonia level. In all of our cases, however, the ammonia values were markedly increased.

Without implying that the disturbance of ammonium metabolism is the only etiologic factor in the pathogenesis of hepatic coma, the finding of persistently high levels in practically every case would logically call for an agent which would have a direct relationship to the metabolism of ammonia. The use of glutamic acid as suggested by Walshe[3] seems rational. Its use is based upon the ability of glutamic acid to combine with ammonia to form glutamine which transports ammonia to the kidney for excretion. It is also deaminated to form alpha-keto glutaric acid which enters the Krebs cycle, thus associating it with carbohydrate metabolism. Glutamic acid has long been known to be of specific importance in the metabolism of the central nervous system.

This report is concerned with the therapeutic evaluation of glutamic acid on the clinical course as well as its relationship to the blood ammonia levels, in patients with hepatic encephalopathies.

Twenty-two patients were studied, all known to have cirrhosis of the liver and all confirmed by liver biopsy, postmortem, or history of previous admissions to the hospital for the same condition.

Ten of the patients were admitted in a state of coma, did not respond to painful stimuli, had absent corneal reflexes and evidences of liver decompensation. Twelve patients were admitted with neurological and mental symptoms such as a clouded sensorium, coarse tremors, slurred speech, confusion, drowsiness, apathy, and disorientation.

Procedure

1. Routine liver function tests were taken and determinations of ammonia levels in both comatose and noncomatose patients were made. In the comatose

patients, an initial dose of 25 gm. of sodium glutamate was given intravenously, as an addition to 500 c.c. of 5 per cent glucose in distilled water.

2. If the patient failed to regain consciousness within a period of six hours, the first dose was repeated three times daily as long as necessary.

3. As soon as the patient regained consciousness, the intravenous sodium glutamate was discontinued and 15 gm. of glutamic acid were given three times daily, either orally or by intragastric drip. This was continued until the mental status of the patient returned to normal.

4. The patient was placed on a low-protein, high carbohydrate diet.

Results

Comatose Group:—In the ten comatose patients, six died in the comatose state. Four survived a total of six episodes of coma. Three of the four subsequently died of hemorrhage, one is still alive. In those cases which survived the initial episode of coma, there was a drop in the ammonia levels with subsequent rise following the advent of a hemorrhage.

TABLE I

Initial Blood Ammonia Levels* in Comatose Group

	F.G.	A.F.	B.G.	C.K.	A.M.	T.P.	E.S.	J.H.	G.L.	L.K.
Age	65	44	57	71	39	48	56	69	37	41
Sex	M	F	F	M	M	F	M	M	F	M
NH_3:	310	445	373	195	230	270	280	335	290	220

*Normal value:
Ammonia 0-60 micrograms per 100 ml. whole blood (method of Conway).

TABLE II

Ammonia Levels in Comatose Group

Name	Age	Sex	NH_3 Levels				Remarks
A.F.	44	F	445	320	280	395	Hemorrhage exitus
L.K.	41	M	220	240	290		Hemorrhage exitus
B.G.	57	F	373	205	170	140	Survived
C.K.	71	M	195	120	280	130	Hemorrhage exitus

TABLE III

BLOOD AMMONIA LEVELS AND LIVER FUNCTION TESTS IN COMATOSE GROUP

Patient	C.K.	B.G.
Total proteins	6.4	5.8
Albumin	2.6	2.8
Globulin	3.8	3.0
Cholesterol	135	240
Cholesterol esters	28	110
Icteric index	81	46
Van den Bergh	PDI	PDI
Cephalin flocculation	4 plus	4 plus
Thymol turbidity	11	14
Prothrombin	35	18
Alkaline phosphatase	24	36
Urea nitrogen	20	18
Blood sugar	85	95
pH	7.35	7.30
Pyruvic acid	2.21	2.10
Ammonia	195–130	373–140

It should be noted that in one of the patients (C. K.), during the comatose state, the ammonia level came down to 130, ten hours before he expired. This may imply that the 130 mcg. did not represent the actual content of the arterial blood since, as has been mentioned, the muscle tissue can remove about 50 per cent of the blood ammonia coming to it. It would also imply the possibility that ammonia is not the only factor in the pathogenesis of hepatic encephalopathy. The liver profile of this patient with particular reference to cholesterol esterification was indicative of marked liver damage. We might add here, that we had similar experiences with noncomatose patients. While the blood ammonia levels were moderately elevated, the liver function tests showed marked functional impairment, and these noncomatose patients also died. On the other hand, patient "B. G.", who survived, showed good cholesterol esterification.

NONCOMATOSE GROUP

The noncomatose group consisted of 12 patients known to have cirrhosis of the liver who were admitted because of marked mental disturbances and the presence of neurological signs. These patients were put on oral glutamic acid 15 gm. three times daily; a daily protein limitation to 50 gm.; and a high

carbohydrate diet. Ammonia levels and liver function tests were done periodically.

TABLE IV

BLOOD AMMONIA LEVELS AND FOLLOW-UP IN NONCOMATOSE GROUP

Name	Age	Sex	Blood Ammonia Levels				Remarks
A.L.	59	M	360	310	205	95	Improved
J.S.	63	F	80	120	195		Coma, exitus
A.W.	72	M	390	270	170	85	Improved
T.W.	50	M	290	95	75		Improved
C.F.	52	M	180	210	110		Improved
H.W.	57	M	290	235	105		Improved
R.W.	41	F	320	200	150	80	Improved
R.T.	49	M	200	128	170	98	Improved
F.J.	61	M	320	190	92		Improved
M.B.	69	F	300	190	210	105	Exitus
E.D.	56	M	260	185	170	95	Coma, exitus
R.P.	60	M	290	210			Coma, exitus

In reviewing the noncomatose group of patients, 8 of the 12 showed marked improvement with complete disappearance of mental symptoms and neurological signs. The remaining four, despite lowering of the ammonia levels, progressed to coma and expired. It should again be noted that all of these four patients showed marked derangement of the liver function tests with particular reference to the cholesterol esterification.

In evaluating our experience with the use of glutamic acid in hepatic coma, we would like to point out that we were primarily interested in three aspects, namely: 1. In the comatose cases to terminate, when possible, the state of coma with the return to consciousness whereby the patient could be given oral supportive treatment.

2. In the noncomatose cases, to restore the normal sensorium with the disappearance of neurological signs.

3. To study the relationship of the blood ammonia levels to the clinical picture.

It would seem that the use of glutamic acid is justified in all cases of hepatic encephalopathy, even in the deeply comatose patients. The termina-

tion of six episodes of coma, irrespective of the subsequent outcome, and the improvement in 8 of 12 noncomatose patients, would imply that glutamic acid had a beneficial effect. While it is true that spontaneous remissions in hepatic coma do take place, we should point out that 3 of the 10 comatose patients had supportive treatment alone for 12 to 24 hours without response, but that they rapidly responded to glutamic acid therapy. What's more, in reviewing a series of cases on the wards of the Metropolitan and Flower-Fifth Avenue

TABLE V

BLOOD AMMONIA LEVELS AND LIVER FUNCTION TESTS IN NONCOMATOSE GROUP

Patient	E.D.	R.P.	M.B.	J.S.
Total proteins	4.8	6.2	4.2	6.8
Albumin	1.8	3.0	1.1	2.4
Globulin	3.0	3.2	3.1	4.4
Cholesterol	125	95	130	85
Cholesterol esters	29	18	38	17
Icteric index	83	45	32	54
Van den Bergh	PDI	PDI	PDI	PDI
Cephalin flocculation	4 plus	4 plus	4 plus	4 plus
Thymol turbidity	7.3	9.5	10.7	7.0
Prothrombin	42	60	41	45
Alkaline phosphatase	34	20	17	47
Urea nitrogen	13	34	28	15
Blood sugar	75	100	140	84
pH	7.36	7.34	7.38	7.39
Pyruvic acid	2.25	2.28	2.21	1.81
Ammonia	260–95	290–210	300–105	80–195

Hospitals before glutamic acid therapy was introduced, there was only one spontaneous remission in 39 cases of hepatic coma.

It should also be emphasized that when a comatose patient was admitted to the hospital, little information was obtainable as to the dietetic regime or medication at home.

In the noncomatose group, the glutamic acid had a marked effect upon lowering the ammonia levels as shown in the tables. Clinically, 8 of the 12 patients were returned to normal sensorium with restored normal neurological

signs. Here again, however, four patients continued a progressively downhill course toward the comatose stage, irrespective of the lowering of the blood ammonia levels. In all four patients, liver function tests showed marked derangement as illustrated by Table V.

Comment

Although, as previously stated, protein or its derivatives can initiate hepatic coma, the actual role of ammonia is still very controversial. Other etiological factors, such as methionine and mercaptans, have been suggested. This is not in accord with clinical experience since these substances are not a usual finding. On the other hand, blood ammonia levels are usually elevated in hepatic coma as reported by various authors[9,10].

It is well known that after absorption of amino acids, deamination occurs in the liver and that the ammonia thus formed is converted to urea. Apparently the failing liver is incapable of urea synthesis, thus resulting in an increase in the blood ammonia. It is therefore logical to decrease the supply of nitrogen sources in severe liver disease. The source of ammonia in a cirrhotic individual may be dietetic from proteins or other nitrogenous matter ingested, from hemorrhage of a ruptured varix, or from absorption of the end products of intestinal bacterial action. Since we are assuming that ammonia plays an important part in the pathogenesis of hepatic encephalopathies, it is logical to use some agent which will metabolize ammonia and permit excretion in the urine. These objectives are accomplished first by reduction of the protein intake, and secondly by glutamic acid which has the ability to combine with ammonia and permit its excretion through the kidney.

The lapsing of four of our noncomatose patients into coma despite a low-protein diet and glutamic acid, and in spite of the lowered blood ammonia levels, implies some other factor than ammonia in the pathogenesis of hepatic coma.

The marked derangement of the liver profile, with particular reference to cholesterol esterification in the above-mentioned cases, would suggest that the degree of the integrity of the liver plays the most important part in the clinical course.

Summary and Conclusion

1. Twenty-two patients with various degrees of hepatic encephalopathies were treated with glutamic acid intravenously and orally. Ten of the cases were comatose and 12 were noncomatose.

2. The effect of glutamic acid on the clinical course and its relationship to the blood ammonia levels was studied.

3. In the comatose group, there was favorable termination of the comatose state in four patients with six episodes of coma.

4. In the noncomatose group, 8 of 12 patients improved mentally and neurologically. There was a direct relationship of the effect of glutamic acid upon the clinical course and the ammonia levels.

5. In 4 of 12 noncomatose patients, the glutamic acid and the low-protein diet produced the reduction of the ammonia levels, but otherwise had no effect on the progressively downhill course.

6. In the above 4 cases the liver profile, as expressed by liver function tests, showed marked derangement. Cholesterol esterification was especially inadequate.

7. Glutamic acid has no intrinsic value in the treatment of liver disease as such, but is a very useful adjunct in the neurological complications of liver disease, permitting gained time to possibly treat the underlying liver pathology.

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Discussion

Dr. Emanuel M. Rappaport (Jamaica, N. Y.):—The management of liver failure is still in a state of flux. Not too many years ago at this convention, in discussing the management of the decompensated liver, I stressed the importance of a high protein intake. It was the vogue at that time to force proteins by whatever channel was available—oral, nasal catheter or intravenous. On

that occasion Dr. Snapper accurately predicted that the then current vogue for this form of therapy would wane, and indeed it has.

The patient who lapses into coma as a result of chronic and progressive liver failure rarely regains consciousness for more than brief moments, regardless of the method of therapy. Of course we can all point to isolated instances of remarkable recovery with various therapeutic agents. I have experienced such recovery from coma with nicotinic acid, and on another occasion with large doses of cortisone. Last week Dr. Gerald Klatskin of Yale Medical School told me of a remarkable restoration of normal sensorium by glutamic acid in a case of coma due to carbon tetrachloride poisoning engrafted upon hepatic cirrhosis.

These are isolated instances and, unfortunately, we rarely repeat our successes in subsequent cases with the same therapy. Since the disturbance of ammonium metabolism is only one of many complex biochemical changes associated with liver failure, there seems to be no reason why the mere lowering of blood ammonium by chemical means should favorably influence the underlying liver damage.

There appears, however, to be a very definite place for glutamic acid in impending coma such as occurs following hemorrhage from varices, and I cannot help but be impressed with the frequent restitution of normal sensorium in such cases, corresponding to the lowering of blood ammonia.

Ammonia intoxication appears to be a specific entity in the encephalopathy of hepatic coma, but recovery is related to the extent of liver damage rather than the ammonium level in the blood. This was emphasized by Dr. Chaikin who pointed out that survival rate was higher in those patients who retained fairly adequate power of esterification. Of course we have seen patients recover with cholesterol esters of zero.

I feel the authors are to be commended for this very fine work and for their conservative perspective relative to the role of ammonia and the therapeutic efficacy of glutamic acid in hepatic coma. What I would like to see, however, is a carefully controlled study of this problem, particularly in patients in the precomatose state, since these are the cases who frequently recover regardless of the method of therapy.

I should like to ask Drs. Chaikin and Konigsberg if they have run into any difficulties with fluid retention or alkalosis, resulting from the large amounts of sodium they employ.

Dr. Samuel L. Immerman (Philadelphia, Pa.):—The metabolic derangements in liver disease are complicated. The Bessmans* believe that a major

*Bessman, S. P. and Bessman, A. N.: J. C. I. **34**:622, 1955.

portion of the oxidative phosphorylation of the brain is derived from the Krebs cycle, and that alpha ketoglutaric acid is the keystone of the structure of this cycle. This substance can combine with ammonia to form glutamic acid, and glutamic acid can further combine with ammonia to form glutamine.

The combination of glutaric acid with ammonia, of course, deprives the brain of glutaric acid. Upon the above basis at least two theories have been advanced to explain the impairment of brain metabolism:

1. ATP, adenosine triphosphate, is necessary for the metabolism of both glucose and glutamic acid; the latter in excess uses ATP and deprives glucose of ATP. For this reason, Pelner† thought glutamate alone might be harmful, and proposed the use of adenosine-5-monophosphate which increases the body stores of ATP.

2. The Bessmans deny that the removal of ATP from an oxidizing system inhibits the system, and they propose a different explanation, viz: that ammonia uses up both brain glutamic acid and brain glutaric acid, in the latter instance interfering with oxidation.

The finding of some increase in the glutamate leaving the brain when ammonia is entering, seems to be corroborative. The high levels of blood ketoglutaric acid, they explain by failure of liver metabolism of fat, protein, and carbohydrate, and by the fact that the brain cannot take up this acid, but normally manufactures its own.

These authors advise the use of alpha-ketoglutaric acid as a therapeutic agent, which would at least act in muscle to combine with ammonia.

On the purely clinical or empirical side, the present authors in their own considerable number of cases appear to have obtained encouraging results with glutamate; however, a total of a large series, together with suitable controls, will be necessary to establish this method of treatment with certainty. A number of workers have expressed disappointment. This includes Schwartz‡, who used 20 gm. of sodium glutamate daily. The present investigators used 25 gm. three times a day. McDermott§ and coworkers felt that glutamate was of value in the exogenous cases, i.e., those due to excess protein, ammonium chloride, and bleeding; that it caused some improvement in the chronic confused state, but had little effect on acutely precipitated spontaneous cases. Various workers have emphasized different aspects in treatment.

The practically constant elevation of blood NH_4 levels in patients with neurologic symptoms seems to indicate that treatment directed to this abnormality may be of paramount importance. With respect to the definition of

†Pelner, L.: J.A.M.A., **162**:63, (1 Sept.), 1956.
‡Schwartz, I. R.: Gastroenterology, **30**:869, (June), 1956.
§McDermott, et al: New England J. Med. **253**:1093, (22 Dec.), 1955.

hepatic coma, Roberts* regards lethargy without hyperventilation and without neurologic signs, as a nonammonia type of hepatic coma. The respiration need not be increased in frequency but is increased in depth.

The blowing off of CO_2 results in respiratory alkalosis, despite the possible decrease of blood electrolytes, and for this Roberts recommends an adequate airway and the administration of 5 to 10 per cent carbon dioxide. For alteration in phosphorous and potassium metabolism he recommended K_2HOP_4 up to 200 mEq. in amounts of 40 mEq. per liter.

Eisman, et al† state that coma accompanied by severe hyponatremia disappears after administration of sodium. Antibiotics have been recommended for an effect on the bowel (decrease of ammonia production) or possibly on the liver. In acute viral hepatitis Ducci and Katz‡ employed antibiotics and cortisone. Glucose, with or without elimination of protein, is part of the treatment.

I might say I think the authors have been very conservative in their own conclusions.

Dr. Nathan W. Chaikin (New York, N. Y.):—We are always very much aware of the sodium problem. As a matter of fact, we always try to give not more than 50 gm. of sodium glutamate intravenously and then continue with glutamic acid by mouth. We have not had many problems due to electrolyte disturbances. Each dose of monosodium glutamate (25 gm.) has about 147 mEq. of sodium. Electrolyte studies were done routinely on all patients and minor adjustments were made where necessary.

Insofar as long-term results are concerned, we have 4 patients who have been kept on a low-protein diet for the past year and a half. I would say that during this time, from a neurological point of view, the symptoms disappeared and all these patients have resumed their usual activities.

*Roberts: M. Clin. North America, **40**:901, (May), 1956.
†Eisman, B. et al: Studies in Ammonia Metabolism. Am. J. Med. **20**:890, 1956.
‡Ducci and Katz: Gastroenterology, **21**:357, 1952.

TUBELESS GASTRIC ANALYSIS*

Evaluation of (Diagnex Improved†) Azure A Carboxylic Resin

SAMUEL S. GILBERT, M.D.
MILTON J. MATZNER, M.D., F.A.C.P., F.A.C.G.
and
I. RICHARD SCHWARTZ, M.D., F.A.C.P., F.A.C.G.
Brooklyn, N, Y.

The use of cation indicator exchange compounds to determine gastric acidity without the necessity of gastric intubation, was first introduced in 1950, by Segal and associates[1]. Further studies and reports[2,3,4,5] have confirmed the efficacy of this technic to detect achlorhydria. The first studies were made using a quininium cation as the exchange resin, which was identified in the urinary excretion after oral ingestion[6]. The knowledge obtained with reference to gastric secretions has been well established[7]. A significant association of achlorhydria and hypochlorhydria with gastric carcinoma has been reported[8]. A ten-year cancer detection survey with screening for achlorhydria by Hitchcock and associates[9] revealed a high incidence of gastric carcinoma in this group. The significance of screening of asymptomatic subjects for achlorhydria and early follow-up diagnosis of gastric cancer has been considered as practical and desirable.

The method and rationale of this tubeless test for gastric acidity and achlorhydria detection, (Figs. 1 and 2) involves the release of an AZO dye (Azure A) cation from the synthetic ion exchange resin by the hydrogen ion in the gastric secretion.

Procedure for Urinalysis

The control and test specimens were subjected to volume, gross color appearance, and pH determinations. The specimens were then diluted with water, the control to 300 ml. and the test specimen to 300 ml. The color of the control specimen was noted and recorded as well as the color of the test specimen (green, blue or absence of color change). Aliquots containing 10 c.c. of the test sample were compared with 10 c.c. aliquots of the standard solution of known concentrations of Azure A. At times, when the test specimen was compared to the standard (blue) it was found necessary to utilize a filter. A 10 c.c. aliquot of the control urine (diluted) which was amber in color, was placed in front of the standard (blue), lessening its color intensity and allow-

*Brooklyn Jewish Hospital and Kings County Hospital in the Division of Gastroenterology—Department of Medicine.
†Diagnex Improved—Supplied by E. R. Squibb & Sons.

ing for a more exact comparison of the unknown. A pH determination was made of both the control and test specimens. Both samples were then acidified with one drop of 18 per cent of hydrochloric acid in order to obtain a pH range between 2 and 4. They were then subjected to a hot water bath for 10 minutes, after which they were allowed to cool. At this point, the test sample was again compared to the known standard. When necessary, the control filter, as noted above, was utilized. A cloudy or turbid test specimen appearing after the water bath, required the addition of a few crystals of aluminum chloride. This sample was then once more subjected to a water bath for 10 minutes, and allowed to cool. The supernatant fluid was then poured off and subjected to

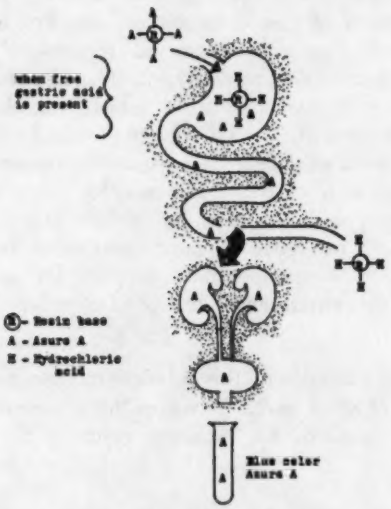

Fig. 1—When free hydrochloric acid is present in the stomach, the Azure A thus released is absorbed from the small intestine. Azure A (blue, green or blue-greenish color) will appear in the urine within two hours after the administration of the resin compound.

a comparison with a known standard[10]. The red pigment in the urine which appeared on boiling the test samples were treated with resin XE-96[13].

Interpretation of Urinary Findings

I. Positive test: Recovery of 0.6 mg. per 300 ml. or more, of Azure A.

Three groups were found in the positive test specimens.

A. The gross undiluted specimens were blue, green or bluish-green in color and were deeper than the standard which contained 0.6 mg. per 300 ml. of Azure A.

B. The samples diluted to 300 ml. still maintained the blue, green or bluish-green color which was deeper than the standard.

C. In the third group both the gross and diluted test specimens were very pale blue or green in color. Routine acidification with one drop of hydrochloric acid and then followed by water bath (procedure for urinalysis) produced a deep change to blue or green-blue in color as in groups A and B.

II. Negative Test: Recovery of 0.3 mg. per 300 ml. of Azure A or less.

Three groups were found in the negative test specimens.

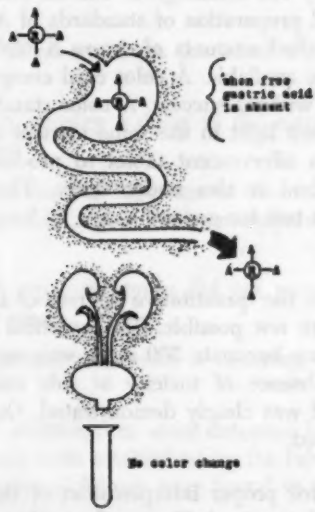

Fig. 2—When no free gastric hydrochloric acid is present in the stomach, the Azure A of the indicator resin is not displaced and none will appear (no color change) in the excreted urine samples for a period of two hours.

A. The gross test specimen failed to show any color change.

B. The diluted specimen acidified and subjected to water bath and cooling, failed to show any change in color from the gross specimen.

C. The diluted specimen, acidified and subjected to a water bath, did produce a change in color, but was found to be less than 0.3 mg. per 300 ml. as compared to standards.

Observations During the Conduct of this Investigation

The detection of a blue color in the undiluted test urine specimen was evident in only 50 per cent of the cases, before they were subjected to acidifica-

tion and water bath heating. By this procedure, the greatest percentage (98 per cent) of positive recoveries were noted and on the basis of this finding, routine acidification and water bath boiling was found to be necessary. It is concluded therefore, that by the above procedure, free Azure A is released from the colorless conjugated form. It was observed that when the test specimens submitted by the patients were colorless or slightly tinted in color, they afforded no clue as to their final determination. For this record it must be stated that test specimens collected after the allowable two hours were not acceptable for determinations. Even known achlorhydrics reported that their urine was markedly blue or green on voiding during the next 24 hours. This has been documented and explained by the exchange of cations other than hydrogen in the small intestine. A careful preparation of standards of Azure A is important and capsules containing specified amounts of Azure A with instructions for proper and easy preparation, are available. A color card comparison chart for use as a standard has been tried without success. A color standard made of transparent plastic, which will transmit light in the same manner as does the test solution, is being developed*. An effervescent tablet to produce heat and replace the water bath boiling method is also under study. These technical assists will further facilitate tubeless test for general usage, in hospital and office screening procedures.

Attempts to correlate the quantitative degrees of free hydrochloric acid by the tubeless method were not possible. The practical value of an oral gastric stimulant (caffeine sodium benzoate 500 mg.) was most satisfactory and without toxic effects. The absence of toxicity or side reactions while taking the Azure A resin compound was clearly demonstrated. On one or two occasions a mild dysuria was reported.

The optimum time for proper interpretation of the submitted urine specimen has not been fully determined. During the early studies, the urine samples were read within 3 to 6 hours after voiding. At present, acidification of the specimen and a delay in reading for a period of 24 to 36 hours has been found desirable. During this period of delay, free Azure A is released from its conjugated form and a more direct positive reading is obtained, without the necessity of the water bath boiling procedure. Those samples that require a water bath heating should be read after a 2-hour cooling period, allowing for proper oxidation.

The utilization of two color standards is deemed desirable in order to screen and detect three groups of cases: 1. Positive groups (Free HCl secretors) 2. Negative groups (Achlorhydria) 3. Intermittent groups (Low acid secretors, hypochlorhydrics, or intermittent acid secretors).

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*Personal communication from the manufacturers, E. R. Squibb and Sons.

Summary of Tests

Ninety-three patients revealed positive evidence of free hydrochloric acid, as noted in Table I by the intubation method. Histamine subcutaneous stimulation for increasing gastric secretions was used, if the fasting samples were found negative by testing with Topfers reagent. The cases subjected to Diagnex tubeless testing (Quinine Carbacrylic Resin) in a previous investigation were also evaluated by this improved tubeless test. Quantitative titrations were not used except in a few instances where low acid secretors were known to exist.

Eighty-seven patients as shown in Table II, gave a positive result with the tubeless Azure A compound. Six cases showing failures were explained as follows:

1. Boiling of the acidified specimen produced a red color due to pigment in the urine.

2. Pyloric obstruction, causing a delay in the emptying time of the gastric contents into the intestine.

3. Vomiting within an hour of ingestion of the resin, causing a failure, due to the absence of absorbable Azure A from appearing in the 2-hour urine sample.

4. Gastrectomy with rapid emptying did not permit a cation exchange to take place in the gastric pouch.

5. Low acid secretor test case with a recovery of less than 0.6 mg. of Azure A (2 cases).

Thirty-nine cases of achlorhydria were detected by the intubation method (Table I). Thirty-six cases were established by the tubeless Azure A compound test (Table II). Three cases of failure were found in this group and explained as follows:

1. Cloudy urine test sample increased in cloudiness after acidification and boiling procedure.

2. Red pigment color change which appeared in the urine test sample, after heating in a water bath.

3. Low acid secretor test case which gave a negative intubation result and in the tubeless test urine, a recovery of less than 0.3 mg. per 300 ml. was found.

On further investigation, methods were developed to mitigate and avoid some of the discrepancies listed as failures, as indicated under procedure.

Comparison of the results of the Tubeless Method (Azure A cation urinary excretion 2 hours after oral ingestion of 2 gm. of indicator) with conventional intubation technic is shown in Tables I and II.

TABLE I

INTUBATION TECHNIC

Secretory Response Histamine Stimulation	Total No. Cases Tested 132	Sex F 54	Sex M 78
Free HCl present	93	29	64
Achlorhydria	39	25	14

TABLE II

TUBELESS METHOD

Azure A cation urinary excretion—2 hours	Total No. Cases Tested 132	Failures	Corrected with Modified Procedure
Free HCl present	87	6	1
Achlorhydria	36	3	2

COMMENT

The study of gastric secretion and detection of achlorhydria by the tubeless method with this compound is moderately simple and feasible without any contraindications. Failures in this indirect method of gastric analysis have been encountered due to changes in the pH of the gastric contents[11]. It has been established that at low levels of gastric secretion, pH change is a much more sensitive index than is measurement of free acid units, by intubation and titration. The inability of the tubeless test to evaluate quantitative degrees of free hydrochloric acid is established[10]. Low acid secretors and variations of gastric secretions in the same individual on different days is constantly reported[12]. Gastric secretory studies other than the determination of the presence or absence of free hydrochloric acid are available. The pepsin tests and radioactive cyanocobalmin determinations may be necessary for futher studies and evaluation. Conventional intubation will be required for cytological studies, and for detection of blood in the gastric contents. Renal excretion defect, hepatic dysfunction, gastrectomy and cases of pyloric obstruction were found and recorded in this survey.

Summary and Interpretation of Present Technic

1. Dilute the 2-hour urine and the control urine specimen with water to 300 ml. If the blue color is equal to or more intense than the 0.6 mg. standard, the patient has secreted free gastric HCl and the test is considered positive.

2. If the blue color is less than the 0.6 mg. standard, pour about 10 c.c. of each diluted urine into two test tubes and add 1 drop of 18 per cent HCl to each aliquot. Then place both test tubes in boiling water for 10 minutes.

a. If the blue color in the 2-hour urine is equal to or more intense than the 0.6 mg. standard, free gastric HCl has been secreted by the patient.

b. A color equal to or less than the 0.3 mg. standard signifies the absence of free gastric HCl.

c. A color between these two standards usually indicates low acid secretion.

d. On the basis of the above, it is possible to establish the need for only one standard. The recovery of 0.6 mg. or more indicates an acid secretor. Those below 0.6 mg. should be considered presumptive achlorhydrics and in general screening surveys as potential cases of anacidity, necessitating repeating of the gastric analysis, including intubation and follow-up scrutiny.

Conclusion

Qualitative estimations of gastric acidity are satisfactory with Azure A compound. Quantitative estimations of free hydrochloric acid by this method are not reliable. Patient participation is relatively simple. This modified and improved test will be extremely useful as a routine screening technic, for hospital and office use, to detect achlorhydria and aid in cancer detection problems.

Acknowledgement

The authors wish to express their appreciation of the technical aid given by Stanley Morgenstern, B.S. and Adelaide Simms, B.A. Department of Biochemistry.

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President's Message

The Membership Policy

Our organization cannot succeed without a strong membership policy. In order to attain membership support a thorough understanding of membership responsibilities is necessary. This knowledge must begin at the grass-roots and extend to the Presidency. An ideal policy must then be characterized by uniformity, regardless of where our members live in the world.

When considering an individual for membership, be sure he is someone you respect for his capabilities as well as his sociability. You should not be embarrassed by having him associate with your family.

The grass-roots of our organization are the General Practitioners. They make up 80 per cent of our doctors. They see at least 80 per cent of gastroenterological problems first. In selecting them for membership, they should have more than the usual interest in gastroenterology. They should also be leaders in their own groups.

Another group eligible for membership are doctors in their residencies, pursuing research, or those who have recently started in the practice of Internal Medicine and who are not yet eligible for their Boards. Many of you must know someone in these categories. In building for strength we must start with eligible young doctors in medicine.

Associate Fellow prospects are those individuals who are eligible for their Specialty Boards but for some reason or other have never become certified. Prospects for Fellowship are men who have their subspecialty Board in Gastroenterology or who are certified in allied specialties such as Internal Medicine, Surgery, Proctology, Pathology, and Radiology.

Now is the time for action and that action should be two prospects for the year from each and everyone of you. This will make our year a successful one and you will have had the satisfaction of having had a part in its success.

Arthur A. Kirchner

Metamucil stimulates normal peristalsis *and* produces soft, easy stools. "Smoothage" management with Metamucil may be continued as long as desired in every type of constipation.

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NEWS NOTES

Residency in Gastroenterology

A residency in gastroenterology, commencing 1 July 1957, is available at the Touro Infirmary in New Orleans, La.

This is an approved residency and further information may be obtained by writing Dr. Murrel H. Kaplan, Chief, Dept. of Gastroenterology, Touro Infirmary, New Orleans, La.

Errata

Through an error, the amount of TLAB in the suppository given to the patient in Case 1 in the article "Rectal Suppository Medication Versus the Oral or Parenteral Route" by Dr. Bernard Weiss, appearing on page 73 of the January 1957 issue was incorrectly stated in two instances.

The correct amount of TLAB in the suppository should be 0.50 mg. This correction will appear in the reprint.

New Fellowship Keys

New Fellowship keys for *Fellows* of the American College of Gastroenterology have been authorized by the Board of Trustees. An illustration of the new key is at the left.

Fellows may order the new keys from the headquarters office, 33 West 60th Street, New York 23, N. Y., at $10.00 each including federal tax and shipping charges.

The reverse side of the key will be engraved with the name and date of election to Fellowship. Send your orders in today.

In Memoriam

We record with profound sorrow the passing of Dr. George E. Pfahler of Philadelphia, Pa., Honorary Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved family.

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Alexander Zabin

GASTROINTESTINAL TRACT

CONCERNING ANEMIA IN PATIENTS WHO HAVE UNDERGONE GASTRECTOMY FOR ULCER: Gerard Rool. Mal. app. Dig., p. 884 (July-Aug.), 1955.

Nonmegaloblastic anemias in patients having undergone gastrectomy reveal a certain number of clinical and biological characteristics. These anemias, particularly frequent if one takes into account latent cases only revealed by certain biological examinations, are connected with deficiency anemias due to fasting.

Actually chalybeate deficiency due to achlorhydria which is often proposed as the cause does not appear to be the essential factor (overloading of the liver in iron, measures of sideremia taken fasting often normal or increased).

In gastrectomized patients disorders in the metabolism of iron are certain, but if these are not the cause of the anemia they too arise from vitamino-protein deficiencies and affect in particular the mechanism of regulation. Biological studies (graphs of hypersideremia induced in gastrectomized patients) anatomical considerations (overloading of the liver in iron in both gastrectomized and pellagrous patients) and experimental findings (study of iron during deficiency caused by fasting in animals, or after exclusion of the pancreas) seem to provide sufficient proof of this point of view.

Guy Albot

INFLAMMATORY LESIONS OF THE ESOPHAGUS AND STOMACH: Fred J. Hodges and Philip Rubin. Am. J. Roentgenol., 74:989 (Dec.), 1955.

To the extent to which the methods employed in roentgenology are reliable in its determination, inflammatory disease occurring in the esophagus and in the stomach is a finding of relative infrequency. Acute and subsequently chronic sclerosing esophagitis following abnormal exposure to acid gastric contents in patients with sliding hiatal hernia is the most commonly recognized form of esophageal inflammatory disease. Luminal narrowing, whether short and high grade or more extensive and less complete, is the most arresting roentgenological finding in esophagitis. The bulk of

confirmed examples of gastritis, as recognizable roentgenologically are of the chronic hypertrophic variety in which the deeper submucosal layers of the stomach are primarily and most extensively involved. The commonest expressions of hypertrophic gastritis as seen by the radiologist are of the localized or segmental variety, usually confined to the extreme lowermost portion of the gastric antrum. Its differentiation from neoplasm is often difficult or impossible. Nonspecific regional inflammatory disease similar in character to lesions found with fair frequency in the small intestine and colon are certainly rarities in the stomach.

FRANZ J. LUST

THE GASTRIC ULCER PROBLEM: E. Clinton Texter, Jr. Illinois M.J., 109:1 (Jan.), 1956.

The problem of gastric ulcer is thoroughly reviewed. Attention is called to the fact that gastric ulcer is a serious problem because of the difficulty in establishing the presence of associated malignancy. History is not typical in most cases. Nausea, vomiting, hemorrhage or gastric pain may be the presenting symptoms. The physical examination is usually negative. Work-up should consist of gastric analysis, stool examination for occult blood, study of the exfoliated gastric cells, gastroscopy and roentgen study. Four cases are presented illustrating the difficulty in differentiating malignant from benign gastric ulcers.

Treatment may be either surgical or medical. In favor of surgical treatment are the need for early surgery to increase survival rate if malignancy is present; the inability to distinguish early between a benign and malignant gastric ulcer; the good results obtained by surgery in treatment of gastric ulcer. In favor of medical management is the ability to distinguish between benign and malignant ulcer by using all diagnostic technics; the low 5-year survival rate suggests that nothing is lost by a several week delay in surgery; operation for gastric ulcer carries a definite mortality risk. The diagnostic error of mistaking benign ulcers for carcinomas and vice versa has been overestimated in the past. Statistics are given to show that the results of medical and surgical treatment are identical.

STANLEY STARK

THE PLACE OF EXTENDED GASTRIC RESECTION IN THE TREATMENT OF GASTRIC MALIGNANCY: Stanley O. Hoerr and George Crile, Jr. Cleveland Clin. Quart., 23:28 (Jan.), 1956.

The authors' caption as extended gastric resection surgery which, while not necessarily including total gastric resection, does imply removal of near-by tissue and/or organs secondarily invaded by the primary malignant process. Enough gastric tissue is removed so that an adequate margin of uninvolved tissue is also resected. Together with the stomach, such additional resection may include: transverse colonic mesentery, the transverse colon, part of the pancreas, spleen, portions of the diaphragm, or left liver lobe.

Gastric malignancy calls for clean excision of the primary tumor together with an adequate margin of uninvolved tissue. This should be done *en bloc* which often requires removal of the greater omentum, areas of lymph drainage from the esophagus downward (including that adjacent to the left gastric artery). If hopeless fixation is not present, all involved structures should be removed as a unit. Such radical surgery is justified where no positive evidence of incurability exists; but distant metastases are a contraindication, as is extension into the roots of the transverse mesocolon, into the celiac axis, or retroperitoneal tissues, or metastases at the *porta hepatis* or to the head of the pancreas.

REGINALD B. WEILER

GASTRIC PHOTOFLUOROGRAPHY: Walter W. Vaughan and Robert J. Reeves. North Carolina M. J., 17:19 (Jan.), 1956.

The first mass gastric survey using a Mobile Gastric Unit was started by the North Carolina State Board of Health in 1949. This paper is a report on the first

10,187 cases using an adapted Schmitt-Helm camera under the table for photofluorography.

Despite the routine of six positioned films the authors conclude that the accuracy of this mass study approaches but does not equal that of a regular gastrointestinal series.

Carcinoma of the stomach has such a poor prognosis at any age that the asymptomatic lesion must be detected if any kind of "cure" is to be hoped for.

They feel that the greatest worth of the photofluorographic method for gastrointestinal tumor detection is not in mass surveys, but in yearly studies of large numbers of patients over 45 years of age.

Initial and follow-up studies when possible convinced 25 of 57 individuals with suspicious findings of malignant lesions to be operated upon. Twenty-one of these 25 were for gastric carcinoma, 6 of these being limited to exploration, ten resections were palliative and only five were curative (no glands at time of operation). Of the other four coming to operation, 2 were carcinomas of the esophagus and 2 were carcinomas of the pancreas.

A. M. SUSINNO

THE MANAGEMENT OF DIVERTICULITIS: Claude E. Welch. Rhode Island M. J., 39:26 (Jan.), 1956.

The presence of diverticula, or diverticulosis, regarded as a degenerative disease, increases with age. Sixty-seven per cent of patients aged 80, show diverticula by x-ray. In a certain percentage of individuals, diverticulitis and the complications, perforation, obstruction and hemorrhage occur. In the absence of diverticulitis, i.e. in the absence of symptoms, surgery is not indicated. The question of interference by surgery is necessary because in the presence of complications the patient must undergo not one, but three operations, viz: 1. colostomy proximal to the lesion, to put the bowel at rest and allow the inflammation to subside; 2. resection of the lesion and 3. closure of the colostomy. On the other hand, early in its course, the lesion can be treated by one operation, resection and end-to-end anastomosis.

With surgery many patients in all groups can be restored to normal health. The operative mortality in recent years has been 2.7 per cent; the mortality from medical treatment 1.0 per cent.

SAMUEL L. IMMERMAN

REFLECTIONS ON THE DIGESTIVE TRACT FROM PULMONARY DISEASE: Charles Cramer. Am. Pract. & Digest Treat. 7:217 (Feb.), 1956.

More than 50 per cent of all cases of gastrointestinal disorders are caused by extraabdominal diseases. In an appreciable portion the primary disturbance is located in the respiratory tract. Direct effects of pulmonary pathology such as metastases from a bronchogenic cancer or mediastinal masses compressing the esophagus must be distinguished from indirect reflections as well as functional disturbances. To the latter group belongs the ileus of pneumonia and the abdominal pain and discomfort from pulmonary infarction, pneumothorax or pleurisy. However, there is no pulmonary disease that produces as many gastrointestinal derangements as pulmonary tuberculosis. Frequently, an incipient tuberculosis or an acute exacerbation of a chronic process produces nothing but anorexia, gas, fullness, nausea, and weight loss.

Three digestive syndromes are especially typical and should alert the physician to watch for pulmonary tuberculosis. 1. The nervous stomach syndrome with irritable weak stomach, heartburn, belching, flatulence, epigastric fullness, intolerance to certain foods and capricious appetite. 2. The pseudoulcer with upper abdominal pain and discomfort and hyperacidity related to food intake. 3. The intestinal flu-syndrome with acute fever, headaches, nausea, diffuse abdominal pain and diarrhea. The cause of the gastrointestinal symptomatology of tuberculosis as well as of other pulmonary diseases is unknown. They are mostly attributed to toxins from the tubercle bacilli as well as to viscerosomatic reflexes.

H. B. EISENSTADT

GASTROINTESTINAL PROBLEMS IN CHRONIC PULMONARY DISEASE: James C. Syner. U. S. Armed Forces M. J., 7:232 (Feb.), 1956.

Gastrointestinal problems arising from systemic toxicity or spreading of a primary pulmonary disorder to the abdomen and vice versa were excluded. Six hundred sixteen patients with various pulmonary diseases such as asthma, emphysema, tuberculosis, bronchiectasis, pulmonary fibrosis, sarcoidosis, carcinoma, fungus disease, etc., were analyzed for their gastrointestinal problems. Symptoms and signs encountered were anorexia, nausea, vomiting, abdominal pain, dysphagia, diarrhea, stomatitis, esophagitis, liver disturbance, hernia, tracheobronchial fistula and ileus. The following factors were found to contribute to the gastrointestinal distress. Swallowing of purulent or malodorous sputum, diminution of taste and smell *fetor ex ore*, retching and vomiting associated with paroxysms of severe coughing, abdominal soreness and pain due to cough, effort breathing interfering with intake of food. However, the greatest number of digestive disturbances were caused by drugs and other therapeutic measures such as chemotherapeutic agents, antibiotics, aminophylline, potassium iodide, cough mixtures, aerosols, pneumoperitoneum and oxygen inhalation.

H. B. Eisenstadt

PROPHYLAXIS AGAINST GASTRIC ULCER: N. B. Jaffe. Med. Times, 84:140 (Feb.), 1956.

This paper gives a summary of all possible conditions which may cause gastric ulcers, stressing especially the viewpoint that the old belief that the gastric contents is sterile is a misunderstanding. There is an unusual number of infectious diseases, constitutional factors, traumatic influences—questions of food influences are discussed. The static influences, with bad postures, working conditions in relation to ulcer formation mentioned. The psychic factors and the general possibility of circulatory influences on the formation of ulcers are stressed.

Helmuth Nathan

INTESTINES

CLOSED-LOOP OBSTRUCTION OF THE ILEUM DUE TO AN APPENDICAL KNOT: Stanley Mikal, Lt. Comdr. and John A. Byers, Lt. (MC) USNR. J.A.M.A., 160:49, (7 Jan.), 1956.

The authors describe the second case so far reported in the literature of ileal obstruction resulting from circumferential strangulation by a diseased appendix. In this case the appendix was weighted down by a mucocele at its tip. The other case reported elsewhere was caused by an appendix the tip of which was a tumorous mass that contained ova of *schistosoma hematobium*.

Wm. K. Billingsley, Jr.

THE PROBLEMS OF ULCERATIVE COLITIS, ILEOSTOMY AND COLECTOMY: Raymond W. McNealy and Caesar Sweitzer. Quart. Bull. Northwestern Univ. M. School 29:383, (Winter), 1955.

Surgical management of ulcerative colitis usually resolves itself into an ileostomy with colectomy. The authors contemplate early surgical intervention for this purpose and give the necessary technic for exacting details in order to place the ileal stoma in the ideal position for management by the patient with least postoperative complication.

Surgical management of ulcerative colitis usually resolves itself into an ileostomy with colectomy. The authors contemplate early surgical intervention for this purpose and give the necessary technic for exacting details in order to place the ileal stoma in the ideal position for management by the patient with least postoperative complication.

Jacob A. Riese

DIFFUSE NODULAR SUBMUCOSAL LIPOMATOSIS OF THE ILEUM: Esther L. Cheatle. Quart. Bull. Northwestern Univ. M. School, 29:330, (Winter), 1955.

A case of diffuse submucosal lipomatosis is presented as an addition to two other similar cases previously reported in the literature. The patient had no symptoms referable to the gastrointestinal tract. Physical examination revealed a cystic mass in the pelvis which was considered to be an ovarian cyst. At laparotomy the mass proved to be adherent loops of enlarged thick-walled ileum. Diffuse nodular lipomatosis involved 75 cm. of the ileum. Large masses of mature fat were present in the submucosa.

JACOB A. RIESE

COLONIC DIVERTICULOSIS: Charles P. McGinty and Carl E. Lischer. Missouri Med., 53:27, (Jan.), 1956.

Colonic diverticulosis usually occurs past middle-age and its etiology is unknown. The author is concerned mainly with the complications and surgical treatment of this condition. He then cites 12 cases illustrating the complications, their treatment and results.

The author suggests the following steps to rule out carcinoma:

1. Barium enema—strictures caused by diverticulitis are longer and have an intact mucosal pattern, while carcinoma leaves a shorter stricture and defect with an interrupted mucosal pattern.

2. Sigmoidoscopy—will not reveal diverticula as they are up too high, but will show carcinoma of the rectosigmoid.

3. Colotomy and sterile endoscopy—is an operative procedure. Colon is opened and a sterile sigmoidoscope is inserted through the colotomy. In diverticula the mucosa is smooth, red, and edematous with a smooth narrowing of the bowel lumen. Biopsy may be taken, but care be observed so as not to spill bowel contents so that tumor will not be transplanted in case of carcinoma.

Types of operation recommended are: 1. Cecostomy—is condemned except where fecal stream is incompletely diverted and inflammatory process will not subside. 2. Colostomy—a. Sigmoid—makes later resection of involved bowel difficult and is to be used only if further resection of bowel is not contemplated. b. Transverse—will completely divert fecal stream but care must be taken to adequately separate the two loops. c. Incision and drainage of abscess, may lead to a fecal fistula. d. One stage resection—of involved portion. This is preferable to 2 or 3 stage method providing certain criteria are met: 1. In presence of peritonitis, cannot do a one stage. 2. In marked inflammation with adhesions of surrounding structures. 3. Intestinal obstruction is a contraindication. 4. Bowel must be adequately prepared. Reasons for doing a primary resection or two: 1. Cannot rule out carcinoma and delay may be fatal. 2. Is easier and less traumatic on the patient. e. Two stage resection—is used where surgeon feels anastomosis is insecure and wants to let it heal while stool is diverted. The colostomy can be closed in 2-3 weeks. f. Three stage operation—must be one in case of a generalized peritonitis, marked inflammation or intestinal obstruction. g. Exteriorization—or obstructive resection is not necessary and is to be condemned.

LOUIS K. MORGANSTEIN

THE USE OF ACTH AND CORTISONE IN IDIOPATHIC ULCERATIVE COLITIS: E. J. Maltby, R. C. Dickson and P. M. O'Sullivan. Canad. M. A. J., 74:4, (1 Jan.), 1956.

Results in the treatment of idiopathic ulcerative colitis between 1930 and 1950 are compared with patients treated in the last five years with ACTH and cortisone. These drugs were used in the latter series of cases for patients with very severe disease; in the patients with early or chronic disease whose conditions had not improved on the usual methods during a trial period they were used as a preoperative measure in patients debilitated by their disease.

The use of ACTH and cortisone in 109 cases of ulcerative colitis was evaluated in the light of previous experiences with the treatment of 205 cases in the two decades prior to the introduction of these hormone preparations. Sixteen per cent in the first series and 32 per cent in the second series

had periods of complete suppression of their disease. The mortality dropped from 38 to 10 per cent and the author feels that the improvement in mortality and morbidity during the past five years is largely due to the introduction of ACTH and cortisone. The improvement during hormone therapy was similar to that which occurred naturally but the response was more rapid and more complete. No serious complications occurred which could be directly attributed to ACTH or cortisone.

JOHN E. COX

AN INTERESTING CASE REPORT OF INTESTINAL OBSTRUCTION DUE TO AN ILEAC FECALITH: K. R. Deibert and W. R. Trapp. J.M.A. Alabama, 25:157, (Jan.), 1956.

A six-year old child was admitted to the hospital with intestinal obstruction approximately 48 hours after eating about 20 pieces of candy which included gum drops and hard suckers of the "jaw breaker" type. On exploration, a hard irregular mass was palpated in the lumen of the lower ileum. This measured about 4½ by 8 cm. and was lodged approximately 12 cm. orad to the ileocecal valve. The mass had caused an intraluminal impaction. The impaction was broken up by gradual fragmentation of the enterolith by the use of rubber shod clamps and an enterotomy was thus avoided.

JOHN M. MCMAHON

INTESTINAL AMEBIASIS. INCIDENCE, SYMPTOMS, AND TREATMENT WITH ARSTHINOL (BALARSEN): Charles H. Brown, William F. Gebhart and Alfred Reich. J.A.M.A., 160:360-363, (4 Feb.), 1956.

Examination of postcathartic fecal specimens was done on an unspecified number of patients residing in the area of Cleveland. The incidence of intestinal amebiasis was found to be 2.1 per cent. The average number of stool examinations per patient is not stated and no mention is made of the use of concentration technics or of stained slides.

In a group of 75 patients with amebiasis the authors find that two-thirds did not have symptoms attributable to the parasitosis. However, they note that many complained of abdominal cramps, gas, history of diarrhea, bloating, and abdominal soreness. Brown, et al apparently consider diarrhea, and cramps in the right lower quadrant to be the only symptoms directly caused by the amebic infection, and they regard other symptoms as nondescript or due to irritable colon. It is difficult to accept this opinion especially since no mention is made of the persistence or disappearance of these ancillary symptoms following their therapy.

A clinical trial of arsthinol (Balarsen®), a trivalent arsenical, was undertaken and the authors were able to treat and subsequently re-examine 31 patients with proved amebiasis. Most of the re-examinations were done one and three months following treatment. The patients had been given five tablets of arsthinol a day for from five to seven days. (The weight of the tablet is not mentioned but presumably is 100 mg.). All of these patients had negative stool findings after treatment. Minimal side-effects were observed at this dosage level. Other workers have reported toxicity following the same or larger doses of this drug.

The authors state that the failure rate of amebacides "in the past" has been about 50 per cent. It is not clear how distant a past is meant, inasmuch as the literature of the last ten years contains many reliable reports of cure rates higher than 80 per cent for all of the accepted amebacides. The authors themselves quote the findings of McHardy and Frye in which cure rates of 91.5 per cent and 83.4 per cent for oxytetracycline and chlortetracycline, respectively, were demonstrated in an extensive study. They also acknowledge a cure rate of 86 per cent with fumagillin.

The impression is given in this report that most amebacides are unsatisfactory but that arsthinol gave excellent results. The findings of numerous careful workers show, however, that although there is no perfect amebacide nine or ten are quite satisfactory for a large majority of cases. The value of arsthinol will be established only after further study.

KERMIT G. DWORK

CLINICAL TRIAL OF GLAUCARUBIN IN TREATMENT OF AMEBIASIS: Efren C. Del Pozo and Manuel Alcaraz. Am. J. Med., 20:412, (March), 1956.

Plants of the genus simarouba have been known to be amebacidal for some time. Recently glaucarubin, a glycoside of Simarouba glauca, has been isolated by Merck and Company. In animal tests this substance was shown to be amebacidal in doses much below those producing toxicity. Therefore, 78 patients with chronic amebiasis and 9 with acute amebic dysentery were treated with a daily dose varying from 10 to 280 mg. for 5 to 32 consecutive days. Dramatic clinical improvement became evident from the first to the sixth day in all persons. Except for occasional nausea, anorexia, diarrhea, no toxicity was encountered, especially no changes of blood counts and liver function tests. Only 2 of the acute and 8 of the chronic cases relapsed.

H. B. EISENSTADT

LIVER AND BILIARY TRACT

INTRAVENOUS CHOLECYSTOCHOLANGIOGRAPHY: William H. Shehadi. J.A.M.A. 159:1350 (3 Dec.), 1955.

The background, chemistry, technic of administration and results of use of Cholografin (sodium iodipamide) in cholecystocholololangiography are reviewed. Its indications are: 1. in patients who have had prior cholecystectomy; 2. when the gallbladder fails to visualize after administration of an orally given radiopaque material; 3. when patients are unable to retain or absorb orally administered dye because of gastrointestinal disease; and 4. when prompt evaluation of the biliary tract is required in acute conditions when surgery is considered.

WM. K. BILLINGSLEY, JR.

TREATMENT OF ACUTE INFECTIOUS HEPATITIS IN THE ARMED FORCES: Thomas C. Chalmers, Wm. E. Reynolds, Richard D. Eckhardt, Joaquin G. Cigarroa, Norman Deane, Robert W. Reifenstein, Clifford W. Smith and Charles S. Davidson. J.A.M.A. 159:1431 (10 Dec.), 1955.

In an effort to determine, by a carefully controlled study, the necessity of prolonged bed rest in the convalescence of hepatitis patients, the commission on liver disease of the Armed Forces Epidemiological Board summarized findings in the recent epidemic of viral hepatitis among military personnel serving in the Far Eastern Theatre of Operations.

Two major study groups were set up by random patient admission. One group followed a strict bed rest throughout the period of hospitalization. The second group was put on an *ad lib* rest routine in which no effort was made to control physical activity.

In another phase of the study one group was subjected to strenuous physical reconditioning as soon as the total serum bilirubin level was 1.5 mg. per 100 c.c. or below. The other group in this study had delayed reconditioning and remained hospitalized an additional 8 days as controls.

In brief the findings indicated that patients treated with *ad lib* rest fared equally well clinically and by laboratory tests with those resting for prolonged periods and could be started on physical reconditioning much earlier because they were not afflicted with the debilitating effects of prolonged rest in bed. These findings are in contradiction to the World War II findings in Germany and these discrepancies are discussed in this article.

As a result of the above studies certain suggested principles of management are outlined for physical rehabilitation of hepatitis patients.

WM. K. BILLINGSLEY, JR.

A SIMPLE MICHROMETHOD FOR DETERMINATION OF BILIRUBIN IN PLASMA: James H. Graham. Am. J. M. Sc. 230:633-635 (Dec.), 1955.

This summarizes a method which seems particularly adaptable in children since venipuncture is not necessary. Heparinized capillary tubes are used to collect the blood.

It is also possible, at the time, to determine the hematocrit and plasma sodium, potassium and chlorides. The method described allows one to find the bilirubin level within 45 minutes.

BERNARD FARFEL

ADRENAL HORMONE THERAPY IN VIRAL HEPATITIS. IV THE EFFECT OF GAMMA GLOBULIN AND ORAL CORTISONE IN THE ACUTE DISEASE: A. S. Evans, R. S. Nelson, H. Sprinz and F. P. Cantrell. Am. J. Med. 19:783-789 (Nov.), 1955.

The authors studied 22 patients with acute viral hepatitis in an attempt to determine if the concurrent administration of gamma globulin would enhance immune mechanisms in patients receiving ACTH or cortisone as therapy. It was found that gamma globulin failed to prevent relapse; four occurred which was an incidence similar to that in the ACTH or cortisone-treated subjects without concurrent gamma globulin therapy. Oral cortisone produced a rapid initial drop in bilirubinemia but failed to influence significantly the total duration of illness except in two patients receiving therapy over a three-week period. Because of increased risks of relapse, and failure to shorten the duration of disease sufficiently, the authors do not feel that cortisone should be recommended for the routine treatment of viral hepatitis, even under ideal circumstances. It may have a place, however, in the treatment of severe and progressive viral hepatitis or in fulminant hepatitis with coma.

JOHN M. MCMAHON

LIVER REGENERATION: ITS MODALITIES AND CONSEQUENCES IN ACUTE DIFFUSE PARENCHYMATOUS HEPATITIS: Guy Albot and Christian Nezelof. Presse medicale 86, (25 Dec.), 1955.

With particular reference to 5 cases the authors describe the histologic picture of liver regeneration with its clinical, biological and pathological consequences in the case of acute diffuse parenchymatous hepatitis.

Repair takes place inside the liver lobule to such areas of regeneration varying in significance according to the extension of the lesions which have provoked them. These areas assume various shapes and involve more or less great part of the lobule, with exclusion of its middle. They temporarily disturb the biliary evacuation and may be a mechanical factor of the intrelobular bile retention in prolonged icterus.

Such defects, due either to extensive damage or to early relapses, or to previous parenchymatous involvement, may hamper the normal regeneration process and incite the cirrhosis process which is caused by abnormal regeneration.

Thus, the ability of hepatic regenerations seems as significant as the purely casual lesion of the hepatitis, for it contributes in "conditioning" not only the importance of the jaundice symptom, but also its duration and possibility of cure.

THE RELATIONSHIP OF CIRRHOSIS OF THE LIVER TO HYPERTENSION: A STUDY OF 504 CASES OF CIRRHOSIS OF THE LIVER: Hubert F. Loyke. Am. J. M. Sc. 230:627-632 (Dec.), 1955.

The author starts with the premise that since we do not have a definite knowledge of the cause of essential hypertension it would be worth studying the circumstances in which hypertension does not occur. A review of the cases admitted during the years of 1943 to 1954 to the St. Alexis and St. John's Hospitals in Cleveland was made. The findings in general show that hypertension does not usually occur with cirrhosis of the liver. It can occur on a physiological basis due to pain. Renal mechanisms may also induce hypertension. Some cases of hypertension which exist in the presense of hepatic disease show a tendency to revert to normal pressures as the hepatic disease advances. As the hypertension returns to normal, it was noted that there is a coincidental reversal of the A/G ratio.

BERNARD FARFEL

POSTOPERATIVE BILE DUCT STRICTURES: Gordon A. Donaldson, Arthur W. Allen and Marshall K. Bartlett. New England J. Med. 254:50 (12 Jan.), 1956.

The authors report 87 benign strictures of the bile ducts from 43 different hospitals. They go into the technical aspects of the surgical procedures which should be of interest to surgeons. They feel most of the strictures are due to the patient's disease at the time of surgery viz: cholecystitis or cholelithiasis. Extravasation of blood and bile are also contributing factors. Methods of corrective surgery are discussed. This report should be studied by all general surgeons.

ABE ALPER

WHAT NOT TO DO IN GALLBLADDER SURGERY: Sir Heneage Ogilvie. Canad. M.A.J. 74:1 (1 Jan.), 1956.

Most disasters of biliary surgery, which are many, usually follow hasty operating in a condition which should never be looked on as an emergency. The author urges us to "Leave the common duct alone." He adds that the common bile duct should be opened if it contains stones, but it should never be explored without good reason. Stones should be removed from the common duct with the greatest tenderness with every effort not to unduly dialate the opening into the duodenum. No chemicals should be introduced. He warns against the use of diathermy on the gallbladder or liver for the reason that there is no finer culture medium known to biological science than cooked liver. He warns against the use of a gallbladder bridge for a pillow to facilitate the operation. Such procedures unduly increase the tension on the anterior abdominal wall and at the same time hyperextend the spine of an elderly patient to a degree that would not be possible except under anesthesia and lead to permanent backache if not to shock.

JOHN E. COX

COMPARATIVE INCIDENCE OF CHOLELITHIASIS IN THE NEGRO AND WHITE RACES: Joseph A. Cummingham and Firmon E. Hardenbergh. A.M.A. Arch. Int. Med. 97:68 (Jan.), 1956.

The over-all incidence of cholelithiasis was studied in the city of Birmingham, Ala. and surrounding territory inhabited by 560,000 people consisting of 60 per cent whites and 40 per cent negroes. Over 6,000 routine autopsies were evaluated. It was concluded that the white race was approximately 4 times as susceptible to cholelithiasis as the negro race with the percentage incidence significantly higher in the female of both races. There was a considerable rise of this disorder with advancing age in the white male as well as the white and colored female, but not in the colored male. Other surveys have shown a similar lower incidence of cholelithiasis not only in negro populations of various parts of the world but also in other pigmented races such as the Bantus of South Africa. The very low number of gallstones in the colored male living in territories with high incidence of enteric infections or general infectious diseases frequently involving the biliary system speaks against Naunyn's theory of the infectious origin of stones. At this time, there is a fairly general agreement that pure cholesterol stones represent an aseptic formation due to bile salt, cholesterol imbalance and calcium bilirubinate stones due to an abnormal bilirubin metabolism. Only mixed gallstones seem to be associated with, but not necessarily caused by infection. There is much less agreement about the role of stasis, pregnancy, obesity, diet and diabetics in the formation of stones.

H. B. EISENSTADT

AMEBIC ABSCESS OF THE LIVER PRESENTING IN THE SUBSCAPULAR AREA: James J. Diamond and Robert A. Scribner. A.M.A. Arch. Int. Med. 97:105 (Jan.), 1956.

The case of a 24-year old male is reported who suffered from an amebic abscess of the liver dissecting extrapleurally into the subcutaneous tissue below the inferior angle of

the right scapula. It appeared as a soft tissue mass shortly after a blunt injury of the thorax. X-ray examination showed not only elevation and immobility of the right hemidiaphragm but also compression deformity of the right pyelogram. Diagnosis was established by the injection of Neo-iopax through a catheter inserted into the fistulous tract found after incision of the subcutaneous abscess. In addition, the sanguino-purulent fluid obtained from the abscess and aspirated through the catheter contained innumerable amebae in the buffy coat after centrifugation. Oral therapy with Aralen, Carbasone and Terramycin was ineffective but continuous irrigation of the cavity with Terramycin solution through 2 catheters led to a complete recovery. Rupture of an amebic abscess has been reported to occur into the right lung, the right pleural cavity, the pericardium, peritoneum, subhepatic and subphrenic space, the lumbar region, stomach, duodenum, colon, *vena cava*, kidney, bile ducts and transdiaphragmatically into the body wall, but never extrapleurally into the subcapular region. This unusual event may have been due to the trauma. A deformity of the right renal pelvis may be caused by a liver abscess without involvement of the kidney or the perirenal tissues.

H. B. EISENSTADT

THE NEW RAPID TEST FOR BILIRUBINURIA: William S. Haubrich. U. Armed Forces M. J., 7:220 (Feb.), 1956.

Bilirubinuria is one of the most consistent findings of acute hepatitis. It is also frequently present in various other biliary diseases. Therefore, a simple rapid test for the detection of this condition is of considerable practical importance. Fifty unselected patients with acute and chronic hepatocellular diseases were repeatedly examined for bilirubinuria with the Ictotest. There was an excellent correlation between this test and the Harrison as well as the Watson-Hawkinson test for bilirubin. There was also a fairly close agreement with the serum bilirubin determination. In performing the Ictotest caution must be exercised to avoid misreading as positive—a faint pink blush—which may appear at the base of the tablet with addition of water, or a color reaction appearing later than 30 seconds. On the average, a positive Ictotest preceded visible jaundice in cases of acute hepatitis by 4 days making early diagnosis as well as treatment possible. Toward the end of the acute hepatitis the bilirubin test remained positive after the visible jaundice had disappeared and even the urine seemed to be already of a normal color. Bilirubinuria cleared shortly before or after the serum bilirubin returned to normal. Therefore, the Ictotest represented a simple method to determine the time of ambulation.

H. B. EISENSTADT

PANCREAS

PANCREATITIS: James J. O'Brien and Theodore R. Thayer. New England J. Med. 253:355 (1 Sept.), 1955.

This is an article dealing with the prognosis and some unusual manifestations of the disease, as seen in 131 cases seen between 1 Jan. 1946, and 31 Dec. 1952, in the West Framingham and Boston Veterans Administration Hospitals. The cases are considered as proven (108), and presumptive (23). This article deals with the 108 proven cases. These are then divided into acute (55) and chronic (53). The cases in this group were proven either at autopsy or at operation. The pathology, etiology, and diagnosis are discussed briefly. In four of the acute cases melena occurred. The laboratory data showed that 65 per cent of the acute cases had an elevated serum amylase if it were done early in the course, but in the chronic cases only 49 per cent showed any elevation of the serum amylase. Thus the authors assume that many cases of acute pancreatitis go unrecognized unless the test is done in the first 24 hours, and in the chronic cases repeatedly.

The treatment in the acute cases was nonsurgical. Aims of treatment were: 1. Suppression of pancreatic function by constant gastric lavage and atropine. 2. Control of pain by Demerol, and less frequently by

procaine blocks. 3. To counteract the infectious components, with penicillin and streptomycin. 4. Adequate fluid and electrolyte replacement; blood plasma and serum albumin, when indicated, and finally, calcium gluconate was given i.v. daily if indicated.

The mortality in the medically treated group was 8 per cent, but 56 per cent of those who recovered from the acute attack had recurrent attacks.

When co-existing gallbladder disease was present and was operated on, the results were good, but when surgery was resorted to, either of necessity, due to some complication, or to mistaken diagnosis, the mortality rate was 4 out of 10 patients. In the treatment of the chronic case surgically, many different surgical procedures were carried out as seemed indicated, but all results were poor. The mortality and recurrence rates were high.

The authors state, "on the basis of this experience, nonsurgical treatment is considered the procedure of choice in an acute attack, or in exacerbation in a chronic case. The recurrence rate is 50 per cent in the patients so treated, but the mortality is lower than that in those operated on as emergencies."

JOHN N. DILL

SYMPOSIUM ON PANCREATITIS: Morton I. Grossman et al. A.M.A. Arch. Int. Med. 96:298-341 (Sept.), 1955.

Experimentally pancreatitis is produced by obstruction of the pancreatic duct, impairment of arterial pancreatic blood supply, forcible injection of bile or other irritants into the pancreatic channels and feeding or parental injections of ethiomine, and antimetabolite destroying pancreatic cells and liberating pancreatic enzymes. The majority of clinical cases follow either biliary disease or excessive intake of alcohol. Differential diagnosis of acute pancreatitis are biliary tract disease, perforated vicus, intestinal obstruction, mesenteric thrombosis and acute myocardial infarction. Jaundice is commonly present in pancreatitis, thrombophlebitis of the leg, rales and friction rubs over the bases of one or both lungs may also be present, abnormal liver function tests are uncommon except a temporary sulfobromophthalein retention. Hypercalcemia and glycosuria occur frequently. Abnormal electrocardiographic tracings may be found without myocardial infarction. Therefore, the enzyme test provides greater assistance during the acute attack in the differentiation between pancreatic and coronary diseases than the electrocardiogram. X-rays show localized gas accumulation in the stomach, small or large bowel located in the left upper abdomen. There might also be an elevation of the diaphragm, atelectasis, pneumonitis, or pleurisy in the basal portions of the lungs. Peroral barium studies performed shortly after subsidence of an acute attack may reveal coarsening of the gastroduodenal folds, an extrinsic pressure defect and displacement of stomach or duodenum. Most useful laboratory tests of pancreatic disease are serum, urinary, and peritoneal fluid amylase and serum lipase, fecal fat and nitrogen after Schmidt diet, glucose tolerance test and plasma antithrombin titer. Medical management consists of control of pain by analgesics, nitrites, intravenous calcium gluconate, parenteral cholinergics and ganglion blocking agents, sympathetic and splanchnic blocks and epidural anesthesia. Furthermore, control of shock and electrolyte imbalance, continuous gastric suction and antibiotics are indicated. Intestinal intubation and insulin injections may be necessary. X-ray therapy has been suggested. There is no agreement about the optimum time for surgical intervention on account of associated biliary disease, uncertainty of clinical diagnosis, and development of complications.

H. B. EISENSTADT

CARCINOMA OF THE PANCREAS AND RELATED STRUCTURES: Robert P. Hohf and James P. Grier. Quart. Bull. Northwestern Univ. M. School 29:223 (Fall), 1955.

The disappointing results in the surgical procedures performed for carcinoma of the pancreas and related structures are discussed. A survey is made of 47 cases. The average longevity following surgery was 12.7 months. The value of surgical resec-

tions for this type of malignancy is open to question. The figures of these authors indicate that the limited resections employed for these tumors, heretofore, have been inadequate as curative procedures but seem to suggest a palliative value.

BERNARD J. FICARRA

THROMBOPHLEBITIS, BLOOD COAGULATION AND PANCREATIC DISEASE: David A. Dreiling, Lester Blum and Martin Sanders. A.M.A. Arch. Int. Med. 96:490 (Oct.), 1955.

Thirty-three patients with thrombosis or thrombophlebitis were examined for pancreatic abnormalities as well as deviations of blood clotting. Nine of them showed abnormal secretin test, blood amylase and antithrombin titer. Two of the latter had pancreatic cancer at the abdominal exploration while the others suffered from chronic pancreatitis. It was shown that chronic inflammation of the pancreas was associated with the same increased tendency to blood clotting as cancer of this organ. Therefore, this abnormal coagulation power must be caused by some disturbance of the pancreatic function and is not a characteristic of the cancer itself. Dissemination of trypsin in the body has been associated with this tendency to clot. However, the mechanism remains obscure. The assumption that hypotrypsinemia reflects increased, and hypertrypsinemia a decreased coagulability, and that the former is observed in association with chronic pancreatic inflammation and cancer, while the latter occurs in acute pancreatic disease is not confirmed by clinical observations. Nevertheless, alteration of the blood trypsin level seems to be in some way associated with abnormal blood clotting.

H. B. EISENSTADT

ADENOMATOSIS OF THE ISLETS OF LANGERHANS: Edwin R. Bickerstaff, Oliver G. Dodge, Arnold Gourevitch and George W. Hearn. Brit. M. J. 4946:997 (22 Oct.), 1955.

A brief review of the literature on adenomatosis of the islets of Langerhans is given, followed by the report of an unusual case. The patient began about ten years prior to this admission, with episodes of "attacks", which became more severe and more frequent. EKG showed very slight changes. Glucose tolerance and fasting blood sugar levels were not remarkable, but it was noted that administration of glucose would bring her out of her "fits". Therefore, long (12-hour) starvation tests were done; the blood sugar fell to 40 mg. per cent, and the EKG showed marked abnormality. This was repeated several times, each giving about the same results. Each time, on being given glucose, she returned to normal. Finally, a subtotal resection of the pancreas was done. The pathological report showed multiple adenomatosis of the gland. After six months, she was better than at any time in the previous ten years, with no "attacks" and a normal EKG.

THE RATIONAL MANAGEMENT OF ACUTE PANCREATITIS: William S. Haubrich. Ohio M. J. 51:1085 (Nov.), 1955.

Until the development of modern determinations of serum amylase and serum lipase, many cases of acute pancreatitis were diagnosed as "acute indigestion", peptic ulcer disease or even liver disease.

In acute pancreatitis the increase in the pancreatic enzymes is attributed to insult of the acinar cells, be it due to bile reflex or ductal metaplasia, the amount of necrosis developing depending on the length of obstruction or amount of pancreatic secretion produced.

After diagnosis, management consists of control of shock by intravenous isotonic glucose or normal saline, with the addition of 4 mg. of norephedrine per 1,000 c.c. as a vasodepressor. Control of pain is by judicial use of centrally acting analgesics, pantopon or demerol, in small doses repeated frequently, and never the use of morphine or codeine.

As the atropine-like effect of demerol and pantopon disappears in large doses, the limit should be 50 mg. of demerol or 10

mg. of pantopon given every 2 hours.

Pancreatic rest should be obtained by use of indwelling catheter, using Wangensteen suction, 90 minutes on, 30 minutes off, neutralizing stomach acidity with aluminum hydroxidemagnesium trisilicate mixture, 10 c.c. every hour, while the suction is operating.

Strict control must be maintained up to 72 hours, when small feedings may be attempted, if the acute symptoms of pain, nausea and vomiting have disappeared.

Atropine in doses of 1/75 gr. should be used often enough to produce "atropinization", in the early stages to bring an inhibition of the parasympathetic impulses.

J. EDWARD BROWN

ACUTE PANCREATITIS: William H. Bristow, Jr. Med. Times 83:1248 (Dec.), 1955.

The author gives a complete resume of the present knowledge of acute pancreatitis, citing the greatest incidence of the condition in males between the ages of 30 and 60 which tends to contradict those who feel that cholesystitis is a factor in etiology of pancreatitis. Cholelithiasis occurs in about 50 per cent of the people with the onset of pancreatitis, usually associated with heavy meals or high alcoholic intake. The diagnosis is based on the severe epigastric pain which is referred to the back, vomiting, muscle rigidity of the abdomen, and general collapse. The diagnosis must be differentiated from other acute surgical conditions by finding of hyperglycemia and increased white blood count, hypocalcemia, serum amylase, and serum lipase studies. The author goes into a rather complete exposition of clinical and laboratory findings, as well as x-ray signs. The etiology is studied under the heading of infection, obstruction of pancreatic duct, chemical irritation, vascular disturbances, and all the other possible causes that have been enunciated over the years. Treatment is conservative, but the various surgical procedures that have been thought of value are described.

JACOB A. RIESE

MARKED HYPOGLYCEMIA ASSOCIATED WITH NONPANCREATIC TUMORS: Richard S. Silvis and Daniel S. Simon. New England J. Med. 254:14 (5 Jan.), 1956.

First, a review of the literature is given. Five cases had been previously reported in which large tumor masses were found, these apparently being the cause of episodes of marked hypoglycemia, although in no case did the tumor mass involve the pancreas. These five patients eventually died, but even at postmortem examination, no pancreatic involvement could be found. The authors then present in detail a sixth case. The patient was a 23-year old male in whom progressive psychic changes had been noted, who was finally admitted to a U. S. Naval hospital for study. He continued to deteriorate until he finally went into coma. Medical studies were then begun, and it was found that he had a large mass in the right flank which was not part of the liver. The only other pertinent findings were a large mass seen on a scout film of the abdomen, in the right upper quadrant, and a blood sugar, while in coma, of 32 mg./100 c.c. Intravenous glucose was given and the patient became responsive. Hypoglycemia was controlled by infusion and lavage, and the patient was operated on. A large tumor mass arising from the right psoas was found. The technical difficulties of the operation are presented in some detail. The patient recovered from the initial surgery, and as the tumor mass was found to be encroaching on the spinal cord, a second operation was done several months later, with removal of the mass through a laminectomy of the 1st and 2nd lumbar vertebrae. From this the patient made an uneventful recovery. Thirteen months later, he was still in good condition. In none of these cases was pancreatic tissue found in the tumor mass, and the authors offer the idea that there is still some mechanism concerned with glucose metabolism that is yet unknown.

JOHN N. DILL

ACUTE PANCREATITIS COMPLICATING DIABETES MELLITUS: Elaine T. Bossak and Robert H. Joelson. A.M.A. Arch. Int. Med. 97:201 (Feb.), 1956.

Eight diabetics, all females, are reported who showed this complication during the course of their disease. The diagnosis of pancreatitis was confirmed either by lapa-

rotomy or by autopsy. Mortality was excessively high, six patients died. In none of them was the diagnosis suspected before death. Amylase is only rarely elevated. Biliary attack or alcoholic bout occasionally precedes the acute catastrophy. The cause of the pancreatitis is unknown but a functional ischemia has been suspected.

H. B. EISENSTADT

PATHOLOGY AND LABORATORY RESEARCH

RECENT FACTS ON THE VASCULARIZATION OF THE GASTRIC PARTITION: G. Cordier, Ch. Debray, J. Thomas and C. Cabrol. La Semaine des Hopitaux 31: (Sept.), 1955.

The authors have applied the technics of injection of plastic substances or solutions opaque to x-rays to the study of the stomach's vessels.

In a series of 40 stomachs, after ligation of all epiploitical vessels and short vessels, the injection is done by the artery then the stomachic coronary vein, injection completed, if necessary, by injection of the artery and the gastroepiploitical right vein. The diffusion of the injected produce is made certain by the anastomosis of the under-mucus plexus and by the circle of two curvatures.

The authors have been able to make use of the lesser curvature's vascularization and the results which have been detailed in the thesis of one of them are the following:

1. They have not noticed considerable anomaly of an aspect with reference to another.

2. The vascular density of the greater curvature is analogous to that of the surfaces.

3. In 10 cases out of 16, one has noted an hypovascularization of the lesser curvature (admirably outlined moreover, on the images which are added to the text). This hypovascularization was not complete, that is to say spread over all the lesser curvature's length in only 2 out of 16. There is almost always only a partial hypovascularization, at the lesser curvature's angle, at the angle and vertical segment, at the angle and horizontal part.

In a second category of conclusions, the authors study the arteriovenous intragastric anastomosis.

The existence of direct arteriovenous anastomosis in the gastric partition has been proved plainly and completes all the series of radiographical, experimental and histological studies which have been made by other authors.

Finally, to broach the pathological problem, the authors study the vascular modifications during ulcers. In an ulcer there exist several kinds of vascular lesions. Next to arterial, venous and capillary lesions which have been known for a long time, the authors emphasize the greater frequency of arteriovenous short circuits with ulcerous people. One can suppose, they say, that these shunts while deriving directly a part of the arterial blood in the veins, may entail an ischemia relative to certain parts of the stomach, this ischemia will favor ulcerations and impede their cicatrization.

GUY ALBOT

STUDIES ON PATHOGENETIC MICROBES IN BONE MARROW IN TYPHOID AND PARATYPHOID: Akira Saito. Tohoku J. Exper. Med. 62:183 (25 Sept.), 1955.

According to the author: "Bone marrow culture is the best for isolation of pathogenetic microbes in typhoid and paratyphoid in comparison with arterial and venous blood, stool, urine and pharyngeal mucus."

The article contains 7 tables which are well laid out and demonstrate the superiority of this method. This is the third report.

This method may be of value in practical differentiation between typhoid, paratyphoid and other febrile diseases. The author's findings would indicate that bone marrow sternal culture yields a much higher percentage of positive findings than cultures of arterial or venous blood.

IRVIN DEUTSCH

CLINICAL AND ROENTGENOLOGIC EVALUATION OF ROUTINE 2 GRAM TELEPAQUE DOSAGE IN CHOLECYSTOGRAPHY: W. M. Whitehouse and O. Martin. Radiology 65:422-424 (Sept.), 1955.

Using a routine 2 gm. dose of Telepaque instead of the routine 3 gm. dose reduced the more common side-effects from an incidence of 37.5 to 33.8 per cent. There was a reduction in the number of extremely dense gallbladder shadows from 59.6 to 46.6 per cent, but the overall decrease of satisfactory (that is excellent or good) diagnostic shadows was only 4 per cent. This is counterbalanced by the decreased likelihood of obscuring biliary calculi by the extremely dense shadows more frequently seen with the 3 gm. dosage. The 2 gm. dosage is satisfactory for the clinically encountered range of patient weights, and no adjustment is generally needed for the heavier patients.

ARNOLD L. BERGER

A COMPARATIVE CLINICAL STUDY OF TERIDAX AND TELEPAQUE IN ROUTINE CHOLECYSTOGRAPHY: W. M. Whitehouse. Radiology 65:425-428 (Sept.), 1955.

A comparison is made of a series of 155 patients receiving 3 gm. of Teridax for routine oral cholecystography with a previous series of 500 patients receiving 2 gm. of Telepaque. The number of patients without side-effects from 3 gm. of Teridax was higher than with 2 gm. of Telepaque; the former giving a slight increase in nausea over the latter, but a considerable decrease in diarrhea. The incidence of dense gallbladder shadows was markedly reduced in comparison with the 2 gm. dose of Telepaque, but the incidence of faintly and nonvisualized gallbladders was more than doubled. However, of 42 patients examined with both contrast media, 8 showed nonvisualization with both, 22 showed denser shadows with Telepaque, 11 similar density and 1 less density. The incidence of contrast media remaining unabsorbed and in the colon is much less with Teridax. Overlying gas in the colon continues to be a problem with both media. Obscuration of opaque stones by dense opacification is a relatively rare occurrence and may be avoided by adequate scout filming before administration of dye.

In the opinion of the author, Telepaque in 2 gm. dosage achieves some reduction in density of the gallbladder shadow and colonic residuum without the more marked reduction in density and colonic residuum seen with Teridax (3 gm.), and these considerations are felt to outweigh the decreased side-effects of Teridax. Telepaque in 2 gm. dosage remains therefore, the routine cholecystographic medium of choice.

ARNOLD L. BERGER

CORNELL CONFERENCE ON THERAPY: CHOICE OF THERAPY IN INTESTINAL PARASITIC DISEASE: Am. J. Med. 19:620 (Oct.), 1955.

This conference, one in a series which has been appearing regularly in the American Journal of Medicine, reviews the treatment of choice in a number of common intestinal parasitic diseases. In intestinal amebiasis, the authors felt that the treatment of choice is a combination of emetine, a broad spectrum antibiotic and an arsenical. Additionally, in cases of recurrence, a halogenated hydroxyquinone derivative such as Diodoquin is indicated. Carriers should receive the same program of treatment as that suggested for acute amebic dysentery. In hepatic amebiasis, the authors do not use chloroquin alone but give it with emetine in alternating courses. Atabrine is the treatment of choice and infestations caused by *giardia lamblia* and tape worm. In pin worm, it is pointed out that since the life of the female worm is about eight weeks, prevention of reinfection for this period could eradicate the disease by hygienic measures alone. However, a combination of these measures with drug, such as terramycin, gentian violet or piperazine citrate is indicated. Enemas are considered ineffective in pin worm infestation.

JOHN M. MCMAHON

BOOK REVIEWS FOR GASTROENTEROLOGISTS

CANCER OF THE LUNG—An Evaluation of the Problem: Proceedings of Scientific Session Annual Meeting, November 3-4, 1953. 322 pages, many illustrations. American Cancer Society, Inc., New York, N. Y., 1956.

This volume on lung cancer should be available to all practicing physicians as a handy reference. It embodies the proceedings of the scientific session at the annual meeting of the American Cancer Society, Inc. Among the contributors to this excellent monograph, one will note the introduction by Dr. Charles S. Cameron, Medical and Scientific Director and Vice-President, American Cancer Society, Inc., Drs. Evarts A. Graham, Bela Halpert, Hans Sustena, John L. Pool, Alton Ochsner and others well known in the realm of cancer. The place of tobacco in the etiology of lung cancer by Drs. Wynder, Hammond and others is discussed by Dr. Gilliam. The use of x-rays in the survey of lung cancer and the alarm and response in cancer of the lung by Dr. Holt and ably discussed by Dr. Cahan, were one of the highlights of the gathering. Cytological examination in the early diagnosis of lung cancer by Dr. Herbert and the newer modalities of irradiation in the treatment of cancer of the lung and treatment of advanced lung cancer by chemical methods, were the final papers of the session.

THE SURGICAL TECHNIC OF ABDOMINAL OPERATIONS: Julius Spivak, M. D., LL.D., F.A.C.S., Associate Professor of Surgery, University of Illinois College of Medicine. Revised—5th Edition: 931 pages, 1037 illustrations on 495 figures, mostly original. Charles C. Thomas, Springfield, Ill., 1955. Price $17.50.

In this massive volume, the author stresses "how to do" rather than "what to do". It is divided into twenty-seven chapters and index. The selected references, as now is the custom, appear at the end of the chapter so that it is easier for the reader to look up additional material by other writers. Reading the clear printed pages and viewing life-like illustrations, one can readily learn to tie a surgical knot as shown on pages 14 and 15. Skimming over the text, the reviewer was pleased to note on page 37, illustrations that the different positions the appendix may assume and the reasons why the diagnosis may be missed. This section in the book should be read by medical men, so that when a patient presents himself with lower abdominal pain without the classical symptoms of appendicitis, one should bear in mind the anomalous positions which the appendix may assume (page 242). In the operative technic, Dr. Spivak points out step by step the various incisions the surgeon may use.

Throughout this instructive volume, the surgeon will find useful information and "how to do it".

THE RELIEF OF SYMPTOMS: Walter Modell, M.D., F.A.C.P., Associate Professor of Clinical Pharmacology, Cornell University Medical College, New York City. 450 Pages. W. B. Saunders Co., Philadelphia, Pa., 1955. Price $8.00.

Dr. Modell, who has been associated with the Department of Pharmacology, Cornell University for the past 20 years, has given us new thoughts for reflection. The reviewer takes this opportunity to congratulate the author on getting away from the stereotyped text of diagnosis and treatment of disease. He stresses the relief of symptoms *per se* and as he claims, this receives scant attention. Maybe I belong to the old school, 50 years of practice, where in my early years we treated symptoms to the exclusion of disease. Fortunately, Dr. Modell realized that symptoms or distress is what the patient came to be treated for and wants immediate relief. In the preface, Dr. Modell states that the book is addressed largely to medical students and to the younger graduates. The reviewer disagrees with this and after careful reading of the text, he feels that the older physician will also greatly benefit from the nuggets which the author disperses throughout the volume.

It would be impossible for the reviewer to single out specific instances in the volume. Therefore, he recommends that Dr. Modell's "Relief of Symptoms" be a necessary acquisition to the physician's library.

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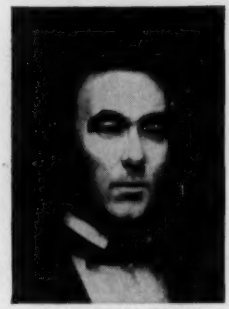

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On the Protein Quality of the Oatmeal Serving

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Tranquilizer with muscle-relaxant action

DISCOVERED AND INTRODUCED BY WALLACE LABORATORIES, *New Brunswick, N. J.*

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U. S. Patent 2,724,720

SUPPLIED: *400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.*

Literature and Samples Available on Request

THE MILTOWN® MEPROBAMATE MOLECULE

CM-3707-R3

EDER-PALMER TRANS-ESOPHAGOSCOPIC FLEXIBLE GASTROSCOPE

Requested by the profession!

Introducing the new Trans-Esophagoscopic Gastroscope and its outstanding features:

1. Designed to fit through our standard 45 or 53 cm by 9.5 mm instruments
2. Smaller in diameter — 9¾ mm but *standard size* lenses — same clarity and brilliant image as known in Eder Gastroscopes.
3. No change or conversion necessary on the Eder-Hufford Flexible Esophagoscope.
4. Longer than the Standard Gastroscopes to permit full advantage of the flexible portion to be felt after it has been passed through the Esophagoscope.
5. Simplifies combination Gastroscopy and Esophagoscopy!
6. Instruments can be used individually or combined!
   One introduction — Two examinations!
7. Patient's discomfort reduced! Doctor's diagnostic areas increased!

For more information, **prices and descriptive folder #89**

Write the manufacturer

EDER INSTRUMENT COMPANY **2293 N. Clybourn Avenue**

Chicago 14, Illinois

Relax the best way ... pause for Coke

continuous quality is quality you trust

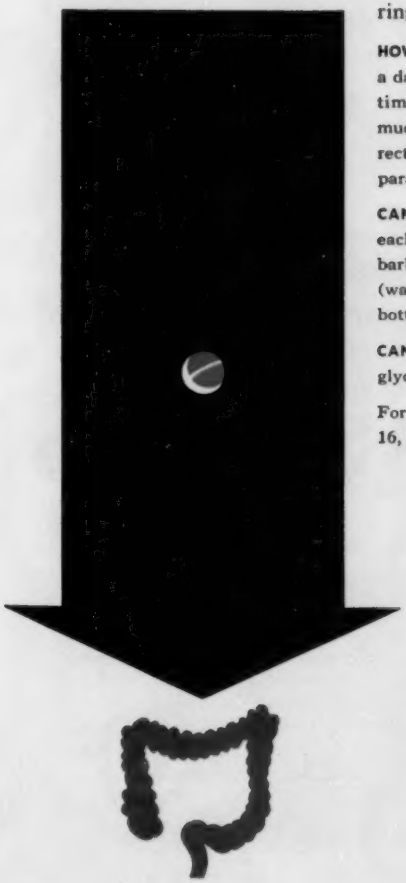
DRINK Coca-Cola

effective, selective therapy

Cantil
for the colon

for functional and organic disorders

CANTIL relieves pain, cramps, bloating...curbs diarrhea...restores normal tone and motility. Selective action focused on the colon avoids widespread interference with normal autonomic function... minimizes urinary retention, mouth dryness, blurring of vision.



HOW CANTIL IS PRESCRIBED One or two tablets three times a day preferably with meals, and one or two tablets at bedtime for patients with ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

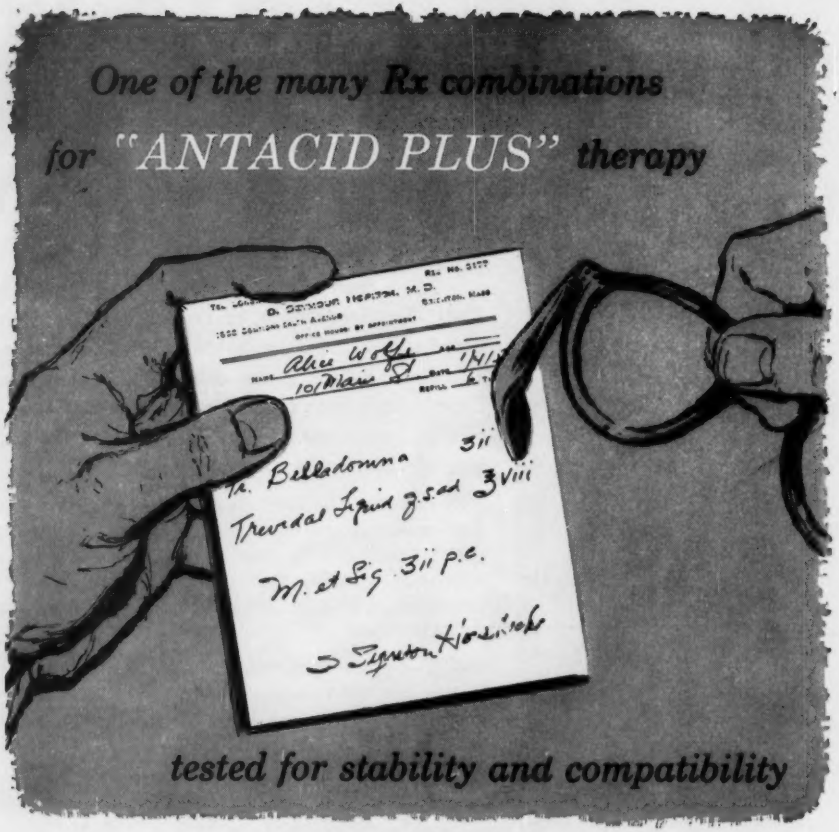
CANTIL—TWO FORMS CANTIL (plain)—25 mg. of CANTIL in each scored tablet—bottles of 100. CANTIL with Phenobarbital—25 mg. of CANTIL and 16 mg. of phenobarbital (warning: may be habit forming) in each scored tablet—bottles of 100.

CANTIL is the *only* brand of N-methyl-3-piperidyl-diphenylglycolate methobromide.

For more detailed information, request Brochure No. NDA 16, Lakeside Laboratories, Milwaukee 1, Wisconsin.

LAKESIDE

14457


One of the many Rx combinations
for "ANTACID PLUS" therapy
Rx
Tr. Belladonna 3ii
Trevidal Liquid q.s.ad 3viii
M. et Sig. 3ii p.c.
tested for stability and compatibility

TREVIDAL® LIQUID

Because you often combine a liquid antacid with other medications, Trevidal Liquid is especially designed for stability and compatibilty in Rx combinations. It has been thoroughly tested with an antispasmodic, sedative, absorbent, antibacterial, costive, carminative, laxative, and digestant. A palatable and effective antacid providing balanced acid neutralization without bowel upsets, Trevidal Liquid makes it easier for you to individualize therapy for your patients by assuring stability and compatibility in your Rxs.

Each Teaspoonful (5 cc) contains:

Aluminum hydroxide	90 mg.
Calcium carbonate	105 mg.
Magnesium trisilicate	150 mg.
Magnesium carbonate	60 mg.
Egraine®*	45 mg.
Regonol®†	35 mg.

Available in 12-oz. bottles

*Binder from oat flour †Vegetable mucin

Organon INC.
ORANGE, N. J.

to NORMALIZE, use KONSYL®

It is important, when inducing normal bowel function, to supply a non-irritating bulk to the colon, especially in those cases in which it has been necessary to eliminate from the diet the high roughage foods containing irritating bulk (lignin and cellulose).

It has been shown[1] that the colon resumes a more normal peristaltic pattern[2] when it is supplied with a stool of medium soft consistency of sufficient bulk[3], especially if the indigestible portion of that bulk consists primarily of hemicellulose.[4]

KONSYL is a vegetable concentrate of naturally occurring hemicelluloses. It is derived from blond psyllium seed and provides just the moist, smooth, effective bulk so essential to normal peristalsis. Its use has been shown to materially hasten the rate of improvement in patients with the irritable colon syndrome.[5] KONSYL contains 100% bulk producing material.

Furthermore, Konsyl is available in 6-ounce and 12-ounce containers at significantly lower-cost-to-patient prices. That's why we say

to NORMALIZE, use KONSYL®

1. Dolkhart, R. E., Dentler, M. & Barrow, L. L., Ill. M. J. 90:286, 1946.
2. Adler, H. F., Atkinson, A. J., & Ivy, A. C., Am. J. Digest. Dis., 8:197, 1941.
3. Wozasek, D., & Stelgman, F., Am. J. Digest. Dis., 9:423, 1942.
4. Williams, R. D., & Olmsted, W. H., Ann. Int. Med., 10:717, 1936.
5. Lieberthal, M. M., Conn. State M. J., 19:86, 1955.

Formula: KONSYL contains 100% platago ovata coating.

Made by BURTON, PARSONS & COMPANY *Since 1939*

Originators of Fine Hydrophilic Colloids

WASHINGTON 9, D. C.

the high cost of bad habits: gastric hyperacidity

Hurried meals and tense days exact their price in short order. Gastric hyperacidity—whether acute or chronic—can, however, be relieved quickly and pleasantly with Gelusil.

Awake or asleep, the patient is protected: The sustained action of magnesium trisilicate and specially prepared aluminum hydroxide gel restores and maintains a mildly acid gastric pH, without overneutralizing or alkalizing. With Gelusil, the twin dangers of acid rebound and systemic alkalosis are thus avoided.

A new formulation, Gelusil-Lac, now combines the proven antacid action of Gelusil with the sustained buffering effect of specially prepared high-protein (low-fat) milk solids. The formula is designed to *prevent* the onset of gastric pain, particularly "middle-of-the-night" attacks.

Nonconstipating: The aluminum hydroxide component in Gelusil assures a low aluminum ion concentration; hence the formation of astringent—and constipating—aluminum chloride is minimal.

Dosage: 2 Gelusil tablets or 2 teaspoonfuls of Gelusil liquid two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel. Gelusil-Lac: at bedtime, one heaping tablespoonful stirred rapidly into one-half glass (4 fl. oz.) of cool water. (Provides equivalent of 4 Gelusil tablets.)

Gelusil®/Gelusil-Lac

WARNER-CHILCOTT

100 YEARS OF SERVICE TO THE MEDICAL PROFESSION